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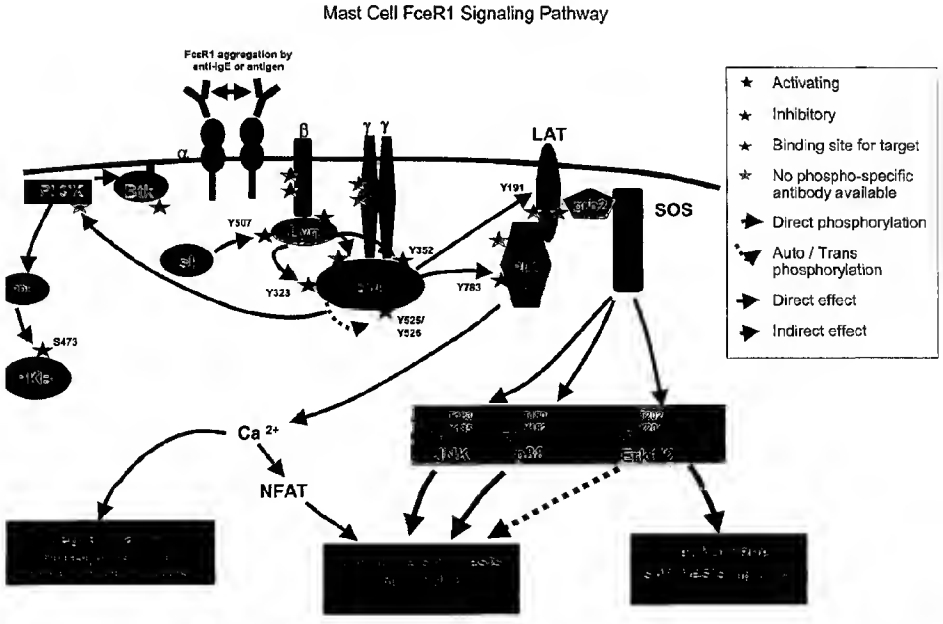
(54) Title: 2,4-PYRIMIDINEDIAMINE COMPOUNDS AND THEIR USES



(57) Abstract: The present invention provides 2,4-pyrimidinediamine compounds that inhibit the IgE and/or IgG receptor signaling cascades that lead to the release of chemical mediators, intermediates and methods of synthesizing the compounds and methods of using the compunds in a variety of contexts, including in the treatment and prevention of diseases characterized by, caused by or associated with the release of chemical mediators *via* degranulation and other processes effected by activation of the IgE and/or IgG receptor signaling cascades.

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2,4–PYRIMIDINEDIAMINE COMPOUNDS AND THEIR USES

1. CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit under 35 U.S.C. § 119(e) to application Serial No. 60/353,333 filed February 1, 2002; application Serial No. 60/353,267 filed February 1, 2002; application Serial No. 60/399,673 filed July 29, 2002; and application Serial No. 60/434,277 filed December 17, 2002.

2. FIELD OF THE INVENTION

The present invention relates generally to 2,4-pyrimidinediamine compounds, pharmaceutical compositions comprising the compounds, intermediates and synthetic methods of making the compounds and methods of using the compounds and compositions in a variety of contexts.

3. BACKGROUND OF THE INVENTION

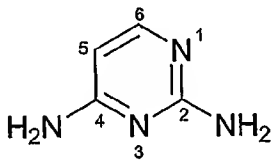
Crosslinking of Fc receptors, such as the high affinity receptor for IgE (FcεRI) and/or the high affinity receptor for IgG (FcγRI) activates a signaling cascade in mast, basophil and other immune cells that results in the release of chemical mediators responsible for numerous adverse events. For example, such crosslinking leads to the release of preformed mediators of Type I (immediate) anaphylactic hypersensitivity reactions, such as histamine, from storage sites in granules *via* degranulation. It also leads to the synthesis and release of other mediators, including leukotrienes, prostaglandins and platelet-activating factors (PAFs), that play important roles in inflammatory reactions. Additional mediators that are synthesized and released upon crosslinking Fc receptors include cytokines and nitric oxide.

The signaling cascade(s) activated by crosslinking Fc receptors such as FcεRI and/or FcγRI comprises an array of cellular proteins. Among the most important intracellular signal propagators are the tyrosine kinases. And, an important tyrosine kinase involved in the signal transduction pathways associated with crosslinking the FcεRI and/or FcγRI receptors, as well as other signal transduction cascades, is Syk kinase (*see* Valent *et al.*, 2002, *Intl. J. Hematol.* 75(4):257-362 for review).

As the mediators released as a result of FcεRI and FcγRI receptor cross-linking are responsible for, or play important roles in, the manifestation of numerous adverse events, the availability of compounds capable of inhibiting the signaling cascade(s) responsible for their release would be highly desireable. Moreover, owing to the critical role that Syk kinase plays these and other receptor signaling cascade(s), the availability of compounds capable of inhibiting Syk kinase would also be highly desirable.

4. SUMMARY OF THE INVENTION

In one aspect, the present invention provides novel 2,4-pyrimidinediamine compounds that, as will be discussed in more detail below, have myriad biological activities. The compounds generally comprise a 2,4-pyrimidinediamine "core" having the following structure and numbering convention:



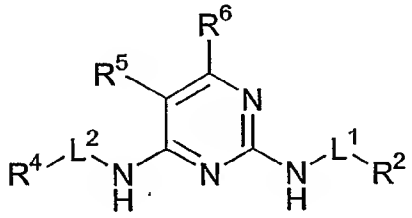
The compounds of the invention are substituted at the C2 nitrogen (N2) to form a secondary amine and are optionally further substituted at one or more of the following positions: the C4 nitrogen (N4), the C5 position and/or the C6 position. When substituted at N4, the substituent forms a secondary amine. The substituent at N2, as well as the optional substituents at the other positions, may range broadly in character and physico-chemical properties. For example, the substituent(s) may be a branched, straight-chained or cyclic alkyl, a branched, straight-chained or cyclic heteroalkyl, a mono- or polycyclic aryl a mono- or polycyclic heteroaryl or combinations of these groups. These substituent groups may be further substituted, as will be described in more detail below.

The N2 and/or N4 substituents may be attached directly to their respective nitrogen atoms, or they may be spaced away from their respective nitrogen atoms *via* linkers, which may be the same or different. The nature of the linkers can vary widely, and can include virtually any combination of atoms or groups useful for spacing one molecular moiety from another. For example, the linker may be an acyclic hydrocarbon bridge (*e.g,* a saturated or unsaturated alkyleno such as methano, ethano, etheno, propano, prop[1]eno, butano, but[1]eno, but[2]eno, buta[1,3]dieno, and the like), a monocyclic or polycyclic hydrocarbon bridge (*e.g.*, [1,2]benzeno, [2,3]naphthaleno, and the like), a simple acyclic heteroatomic or

heteroalkyldiyl bridge (*e.g.*, -O-, -S-, -S-O-, -NH-, -PH-, -C(O)-, -C(O)NH-, -S(O)-, -$S(O)_2$-, -S(O)NH-, -$S(O)_2$NH-, -O-CH_2-, -CH_2-O-CH_2-, -O-CH=CH-CH_2-, and the like), a monocyclic or polycyclic heteroaryl bridge (*e.g.*, [3,4]furano, pyridino, thiopheno, piperidino, piperazino, pyrazidino, pyrrolidino, and the like) or combinations of such bridges.

The substituents at the N2, N4, C5 and/or C6 positions, as well as the optional linkers, may be further substituted with one or more of the same or different substituent groups. The nature of these substituent groups may vary broadly. Non-limiting examples of suitable substituent groups include branched, straight–chain or cyclic alkyls, mono- or polycyclic aryls, branched, straight–chain or cyclic heteroalkyls, mono- or polycyclic heteroaryls, halos, branched, straight–chain or cyclic haloalkyls, hydroxyls, oxos, thioxos, branched, straight-chain or cyclic alkoxys, branched, straight-chain or cyclic haloalkoxys, trifluoromethoxys, mono- or polycyclic aryloxys, mono- or polycyclic heteroaryloxys, ethers, alcohols, sulfides, thioethers, sulfanyls (thiols), imines, azos, azides, amines (primary, secondary and tertiary), nitriles (any isomer), cyanates (any isomer), thiocyanates (any isomer), nitrosos, nitros, diazos, sulfoxides, sulfonyls, sulfonic acids, sulfamides, sulfonamides, sulfamic esters, aldehydes, ketones, carboxylic acids, esters, amides, amidines, formadines, amino acids, acetylenes, carbamates, lactones, lactams, glucosides, gluconurides, sulfones, ketals, acetals, thioketals, oximes, oxamic acids, oxamic esters, etc., and combinations of these groups. Substituent groups bearing reactive functionalities may be protected or unprotected, as is well-known in the art.

In one illustrative embodiment, the 2,4-pyrimidinediamine compounds of the invention are compounds according to structural formula (I):



including salts, hydrates, solvates and N-oxides thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted

with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$; $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a, R^b, R^a substituted with one or more of the same or different R^a or R^b, $-OR^a$ substituted with one or more of the same or different R^a or R^b, $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$, $-S-(CH_2)_m-R^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$, $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of =O, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, =S, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently a protecting group or R^a, or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which may optionally be substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently a protecting group or R^a;

each *m* is independently an integer from 1 to 3; and

each *n* is independently an integer from 0 to 3.

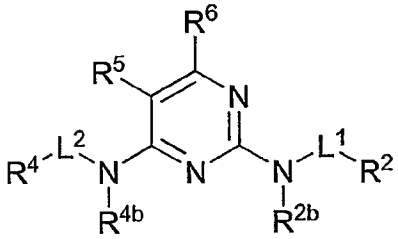
In another aspect, the present invention provides prodrugs of the 2,4-pyrimidinediamine eompounds. Such prodrugs may be active in their prodrug form, or may be inactive until converted under physiological or other conditions of use to an active drug

form. In the prodrugs of the invention, one or more functional groups of the 2,4-pyrimidinediamine compounds are included in promoieties that cleave from the molecule under the conditions of use, typically by way of hydrolysis, enzymatic cleavage or some other cleavage mechanism, to yield the functional groups. For example, primary or secondary amino groups may be included in an amide promoiety that cleaves under conditions of use to generate the primary or secondary amino group. Thus, the prodrugs of the invention include special types of protecting groups, termed "progroups," masking one or more functional groups of the 2,4-pyrimidinediamine compounds that cleave under the conditions of use to yield an active 2,4-pyrimidinediamine drug compound. Functional groups within the 2,4-pyrimidinediamine compounds that may be masked with progroups for inclusion in a promoiety include, but are not limited to, amines (primary and secondary), hydroxyls, sulfanyls (thiols), carboxyls, carbonyls, phenols, catechols, diols, alkynes, phosphates, etc. Myriad progroups suitable for masking such functional groups to yield promoieties that are cleavable under the desired conditions of use are known in the art. All of these progroups, alone or in combinations, may be included in the prodrugs of the invention. Specific examples of promoieties that yield primary or secondary amine groups that can be included in the prodrugs of the invention include, but are not limited to amides, carbamates, imines, ureas, phosphenyls, phosphoryls and sulfenyls. Specific examples of promoieties that yield sulfanyl groups that can be included in the prodrugs of the invention include, but are not limited to, thioethers, for example S-methyl derivatives (monothio, dithio, oxythio, aminothio acetals), silyl thioethers, thioesters, thiocarbonates, thiocarbamates, asymmetrical disulfides, etc. Specific examples of promoieties that cleave to yield hydroxyl groups that can be included in the prodrugs of the invention include, but are not limited to, sulfonates, esters and carbonates. Specific examples of promoieties that yield carboxyl groups that can be included in the prodrugs of the invention included, but are not limited to, esters (including silyl esters, oxamic acid esters and thioesters), amides and hydrazides.

In one illustrative embodiment, the prodrugs of the invention are compounds according to structural formula (I) in which the protecting group of R^c and R^d is a progroup.

Replacing the hydrogens attached to N2 and N4 in the 2,4-pyrimidinediamines of structural formula (I) with substituents adversely affects the activity of the compounds. However, as will be appreciated by skilled artisans, these nitrogens may be included in promoieties that, under conditions of use, cleave to yield 2,4-pyrimidinediamines according

to structural formula (I). Thus, in another illustrative embodiment, the prodrugs of the invention are eompounds according to structural formula (II):



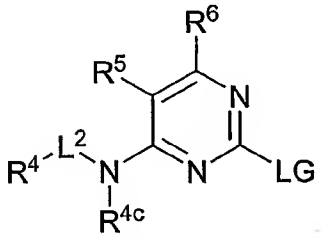
including salts, hydrates, solvates and N-oxides thereof, wherein:

R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for structural formula (I); and

R^{2b} and R^{4b} are each, independently of one another, a progroup.

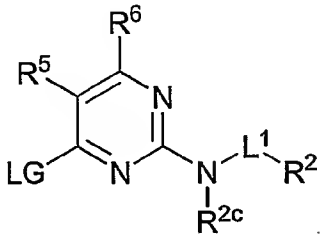
In another aspect, the present invention provides compositions comprising one or more compounds and/or prodrugs of the invention and an appropriate carrier, excipient or diluent. The exact nature of the carrier, excipient or diluent will depend upon the desired use for the composition, and may range from being suitable or acceptable for veterinary uses to being suitable or acceptable for human use.

In still another aspect, the present invention provides intermediates useful for synthesizing the 2,4-pyrimidinediamine compounds and prodrugs of the invention. In one embodiment, the intermediates are 4-pyrimidineamines according to structural formula (III):



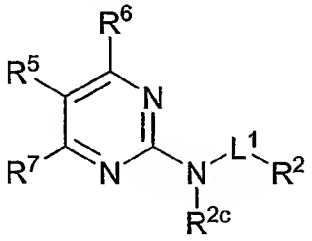
including salts, hydrates, solvates and N-oxides thereof, wherein R^4, R^5, R^6 and L^2 are as previously defined for structural formula (I); LG is a leaving group such as, for example, $-S(O)_2Me$, -SMe or halo (*e.g.*, F, Cl, Br, I); and R^{4c} is hydrogen or a progroup.

In another embodiment, the intermediates are 2-pyrimidineamines according to structural formula (IV):



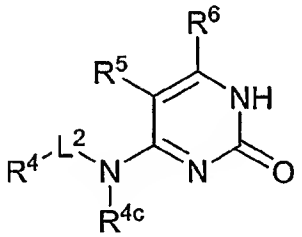
including salts, hydrates, solvates and N-oxides thereof, wherein R^2, R^5, R^6 and L^1 are as previously defined for structural formula (I); LG is a leaving group, such as, for example, $-S(O)_2Me$, -SMe or halo (*e.g.*, F, Cl, Br, I) and R^{2c} is hydrogen or a progroup.

In yet another embodiment, the intermediates are 4-amino- or 4-hydroxy-2-pyrimidineamines according to structural formula (V):



including salts, hydrates, solvates and N-oxides thereof, wherein R^2, R^5, R^6 and L^1 are as previously defined for structural formula (I), R^7 is an amino or hydroxyl group and R^{2c} is hydrogen or a progroup.

In another embodiment, the intermediates are N4-substituted cytosines according to structural formula (VI):



including salts, hydrates, solvates and N-oxides thereof, wherein R^4, R^5, R^6 and L^2 are as previously defined for structural formula (I) and R^{4c} is hydrogen or a progroup.

In yet another aspect, the present invention provides methods of synthesizing the 2,4-pyrimidinediamine compounds and prodrugs of the invention. In one embodiment, the method involves reacting a 4-pyrimidineamine according to structural formula (III) with an amine of the formula $HR^{2c}N\text{-}L^1\text{-}R^2$, where L^1, R^2 and R^{2c} are as previously defined for structural formula (IV) to yield a 2,4-pyrimidinediamine according to structural formula (I) or a prodrug according to structural formula (II).

In another embodiment, the method involves reacting a 2-pyrimidineamine according to structural formula (IV) with an amine of the formula $R^4\text{-}L^2\text{-}NHR^{4c}$ where L^4, R^4 and R^{4c} are as previously defined for structural formula (III) to yield a 2,4-

pyrimidinediamine according to structural formula (I) or a prodrug according to structural formula (II).

In yet another embodiment, the method involves reacting a 4-amino-2-pyrimidineamine according to structural formula (V) (in which R^7 is an amino group) with an amine of the formula R^4-L^2-NHR^{4c}, where L^2, R^4 and R^{4c} are as defined for structural formula (III), to yield a 2,4-pyrimidinediamine according to structural formula (I) or a prodrug according to structural formula (II). Alternatively, the 4-amino-2-pyrimidineamine may be reacted with a compound of the formula R^4-L^2-LG, where R^4 and L^2 are as previously defined for structural formula (I) and LG is a leaving group.

In still another embodiment, the method involves halogenating a 4-hydroxy-2-pyrimidineamine according to structural formula (V) (R^7 is a hydroxyl group) to yield a 2-pyrimidineamine according to structural formula (IV) and reacting this pyrimidineamine with an appropriate amine, as described above.

In yet another embodiment, the method involves halogenating an N4-substituted cytosine according to structural formula (VI) to yield a 4-pyrimidineamine according to structural formula (III) and reacting this pyrimidineamine with an appropriate amine, as described above.

The 2,4-pyrimidinediamine compounds of the invention are potent inhibitors of degranulation of immune cells, such as mast, basophil, neutrophil and/or eosinophil cells. Thus, in still another aspect, the present invention provides methods of regulating, and in particular inhibiting, degranulation of such cells. The method generally involves contacting a cell that degranulates with an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit degranulation of the cell. The method may be practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with cellular degranulation.

While not intending to be bound by any theory of operation, biochemical data confirm that the 2,4-pyrimidinediamine compounds exert their degranulation inhibitory effect, at least in part, by blocking or inhibiting the signal transduction cascade(s) initiated by crosslinking of the high affinity Fc receptors for IgE ("FcεRI") and/or IgG ("FcγRI"). Indeed, the 2,4-pyrimidinediamine compounds are potent inhibitors of both FcεRI-mediated and FcγRI-mediated degranulation. As a consequence, the 2,4-pyrimidine compounds may be used to inhibit these Fc receptor signalling cascades in any cell type expressing such

FcεRI and/or FcγRI receptors including but not limited to macrophages, mast, basophil, neutrophil and/or eosinophil cells.

The methods also permit the regulation of, and in particular the inhibition of, downstream processes that result as a consequence of activating such Fc receptor signaling cascade(s). Such downstream processes include, but are not limited to, FcεRI-mediated and/or FcγRI-mediated degranulation, cytokine production and/or the production and/or release of lipid mediators such as leukotrienes and prostaglandins. The method generally involves contacting a cell expressing an Fc receptor, such as one of the cell types discussed above, with an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvent, N-oxide and/or composition thereof, effective to regulate or inhibit the Fc receptor signaling cascade and/or a downstream process effected by the activation of this signaling cascade. The method may be practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with the Fc receptor signaling cascade, such as diseases effected by the release of granule specific chemical mediators upon degranulation, the release and/or synthesis of cytokines and/or the release and/or synthesis of lipid mediators such as leukotrienes and prostaglandins.

In yet another aspect, the present invention provides methods of treating and/or preventing diseases characterized by, caused by or associated with the release of chemical mediators as a consequence of activating Fc receptor signaling cascades, such as FcεRI and/or FcγRI- signaling cascades. The methods may be practiced in animals in veterinary contexts or in humans. The methods generally involve administering to an animal subject or human an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to treat or prevent the disease. As discussed previously, activation of the FcεRI or FcγRI receptor signaling cascade in certain immune cells leads to the release and/or synthesis of a variety of chemical substances that are pharmacological mediators of a wide variety of diseases. Any of these diseases may be treated or prevented according to the methods of the invention.

For example, in mast cells and basophil cells, activation of the FcεRI or FcγRI signaling cascade leads to the immediate (*i.e.*, within 1-3 min. of receptor activation) release of preformed mediators of atopic and/or Type I hypersensitivity reactions (*e.g.*, histamine, proteases such as tryptase, etc.) *via* the degranulation process. Such atopic or Type I hypersensitivity reactions include, but are not limited to, anaphylactic reactions to

environmental and other allergens (*e.g.*, pollens, insect and/or animal venoms, foods, drugs, contrast dyes, etc.), anaphylactoid reactions, hay fever, allergic conjunctivitis, allergic rhinitis, allergic asthma, atopic dermatitis, eczema, urticaria, mueosal disorders, tissue disorders and eertain gastrointestinal disorders.

The immediate release of the preformed mediators *via* degranulation is followed by the release and/or synthesis of a variety of other chemical mediators, including, among other things, platelet activating factor (PAF), prostaglandins and leukotrienes (e.g., LTC4) and the *de novo* synthesis and release of cytokines such as TNFα, IL-4, IL-5, IL-6, IL-13, etc. The first of these two processes occurs approximately 3-30 min. following receptor activation; the latter approximately 30 min. – 7 hrs. following receptor activation. These "late stage" mediators are thought to be in part responsible for the chronic symptoms of the above-listed atopic and Type I hypersensitivity reactions, and in addition are chemical mediators of inflammation and inflammatory diseases (e.g., osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, idiopathic inflammatory bowel disease, irritable bowel syndrome, spastic colon, etc.), low grade scarring (e.g., scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction), and sicca complex or syndrome. All of these diseases may be treated or prevented according to the methods of the invention.

Additional diseases which can be treated or prevented according to the methods of the invention include diseases associated with basophil cell and/or mast cell pathology. Examples of such diseases include, but are not limited to, diseases of the skin such as scleroderma, cardiac diseases such as post myocardial infarction, pulmonary diseases such as pulmonary muscle changes or remodeling and chronic obstructive pulmonary disease (COPD) and diseases of the gut such as inflammatory bowel syndrome (spastic colon).

The 2,4-pyrimidinediamine compounds of the invention are also potent inhibitors of the tyrosine kinase Syk kinase. Thus, in still another aspect, the present invention provides methods of regulating, and in particular inhibiting, Syk kinase activity. The method generally involves contacting a Syk kinase or a cell comprising a Syk kinase with an amount of a 2,4-pyrimidinediamine compound or prodrug of the invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit Syk kinase activity. In one embodiment, the Syk kinase is an isolated or recombinant Syk kinase. In another embodiment, the Syk kinase is an endogenous or recombinant Syk kinase expressed by a cell, for example a mast cell or a basophil cell. The method may be

practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or assoeiated with Syk kinase activity.

While not intending to be bound by any particular theory of operation, it is believed that the 2,4-pyrimdinediamine compounds of the invention inhibit cellular degranulation and/or the release of other chemical mediators primarily by inhibiting Syk kinase that gets activated through the gamma chain homodimer of FcεRI (*see, e.g.,* FIG. 2). This gamma chain homodimer is shared by other Fc receptors, including FcγRI, FcγRIII and FcαRI. For all of these receptors, intracellular signal transduction is mediated by the common gamma chain homodimer. Binding and aggregation of those receptors results in the recruitment and aetivation of tyrosine kinases such as Syk kinase. As a consequence of these common signaling activities, the 2,4-pyrimidinediamine compounds described herein may be used to regulate, and in particular inhibit, the signaling cascades of Fc receptors having this gamma chain homodimer, such as FcεRI, FcγRI, FcγRIII and FcαRI, as well as the cellular responses elicited through these receptors.

Syk kinase is known to play a critical role in other signaling cascades. For example, Syk kinase is an effector of B-cell receptor (BCR) signaling (Turner *et al.,* 2000, Immunology Today 21:148-154) and is an essential component of integrin beta(1), beta(2) and beta(3) signaling in neutrophils (Mocsai *et al.,* 2002, Immunity 16:547-558). As the 2,4-pyrimidinediamine compounds described herein are potent inhibitors of Syk kinase, they can be used to regulate, and in particular inhibit, any signaling cascade where Syk plays a role, such as, fore example, the Fc receptor, BCR and integrin signaling cascades, as well as the cellular responses elicited through these signaling cascades. The particular cellular response regulated or inhibited will depend, in part, on the specific cell type and receptor signaling cascade, as is well known in the art. Non-limiting examples of cellular responses that may be regulated or inhibited with the 2,4-pyrimidinediamine compounds include a respiratory burst, cellular adhesion, cellular degranulation, cell spreading, cell migration, phagocytosis (*e.g.,* in macrophages), calcium ion flux (*e.g.,* in mast, basophil, neutrophil, eosinophil and B-cells), platelet aggregation, and cell maturation (*e.g.,* in B-cells).

Thus, in another aspect, the present invention provides methods of regulating, and in particular inhibiting, signal transduction cascades in which Syk plays a role. The method generally involves eontacting a Syk-dependent receptor or a cell expressing a Syk-dependent receptor with an amount of a 2,4-pyrimidinediamine compound or prodrug of the

invention, or an acceptable salt, hydrate, solvate, N-oxide and/or composition thereof, effective to regulate or inhibit the signal transduction cascade. The methods may also be used to regulate, and in particular inhibit, downstream processes or cellular responses elicited by activation of the particular Syk-dependent signal transduction cascade. The methods may be practiced to regulate any signal trasduction cascade where Syk is not known or later discovered to play a role. The methods may be practiced in *in vitro* contexts or in *in vivo* contexts as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by or associated with activation of the Syk-dependent signal transduction cascade. Non-limited examples of such diseases include those previously discussed.

5. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 provides a cartoon illustrating allergen-induced production of IgE and consequent release of preformed and other chemical mediators from mast cells;

FIG. 2 provides a cartoon illustrating the FcεR1 signal transduction cascade leading to degranulation of mast and/or basophil cells;

FIG. 3 provides a cartoon illustrating the putative points of action of compounds that selectively inhibit upstream FcεRI-mediated degranulation and compounds that inhibit both FcεRI-mediated and ionomycin-induced degranulation;

FIG. 4 provides graphs illustrating the effects of certain 2,4-pyrimidinediamine compounds, DMSO (control) and ionomycin on Ca^{2+} flux in CHMC cells;

FIG. 5 provides graphs illustrating the immediacy of the inhibitory activity of compounds R921218 and R926495;

FIG. 6 provides a graph illustrating the effect of washout on the inhibitory activity of compounds R921218 and R921302;

FIG. 7 provides data showing that varying concentrations of compounds R921218 (A) and R921219 (B) inhibit phosporylation of various proteins downstream of Syk kinase in the IgE receptor signal transduction cascade in activated BMMC cells;

FIG. 8 provides data showing dose responsive inhibition of Syk kinase phosphorylation of an endogenous substrate (LAT) and a peptide substrate in the presence of increasing concentrations of compounds R921218 (X), R921219 (Y) and R921304 (Z);

FIG. 9 provides data showing that the inhibition of Syk kinase by compound R921219 is ATP competitive;

FIG. 10 provides data showing that varying concentrations of compounds R921219 (A) and R218218 (B) inhibit phosphorylation of proteins downstream of Syk kinase, but not LYN kinase, in the FcεRI signal transduction cascade in activated CHMC cells; also shown is inhibition of phosphorylation of proteins downstream of LYN kinase but not Syk kinase, in the presence of a known LYN kinase inhibitor (PP2); and

FIGS. 11A-D provide data showing inhibition of phosphorylation of proteins downstream of Syk kinase in the FcεRI signal transduction cascade in BMMC cells.

6. DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

6.1 Definitions

As used herein, the following terms are intended to have the following meanings:

"Alkyl" by itself or as part of another substituent refers to a saturated or unsaturated branched, straight-chain or cyclic monovalent hydrocarbon radical having the stated number of carbon atoms (*i.e.*, C1-C6 means one to six carbon atoms) that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl , prop-2-yn-1-yl, etc.; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature "alkanyl," "alkenyl", and/or "alkynyl" is used, as defined below. In preferred embodiments, the alkyl groups are (C1-C6) alkyl.

"Alkanyl" by itself or as part of another substituent refers to a saturated branched, straight-chain or cyclic alkyl derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (*t*-butyl), cyclobutan-1-yl, etc.; and the like. In preferred embodiments, the alkanyl groups are (C1-C6) alkanyl.

"Alkenyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl , prop-1-en-2-yl, prop-2-en-1-yl, prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl ; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, etc.; and the like. In preferred embodiments, the alkenyl group is (C2-C6) alkenyl.

"Alkynyl" by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl , prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl , etc.; and the like. In preferred embodiments, the alkynyl group is (C2-C6) alkynyl.

"Alkyldiyl" by itself or as part of another substituent refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon group having the stated number of carbon atoms (*i.e.*, C1-C6 means from one to six carbon atoms) derived by the removal of one hydrogen atom from each of two different carbon atoms of a parent alkane, alkene or alkyne, or by the removal of two hydrogen atoms from a single carbon atom of a parent alkane, alkene or alkyne. The two monovalent radical centers or each valency of the divalent radical center can form bonds with the same or different atoms. Typical alkyldiyl groups include, but are not limited to, methandiyl; ethyldiyls such as ethan-1,1-diyl, ethan-1,2-diyl, ethen-1,1-diyl, ethen-1,2-diyl; propyldiyls such as propan-1,1-diyl, propan-1,2-diyl, propan-2,2-diyl, propan-1,3-diyl, cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, prop-1-en-1,1-diyl, prop-1-en-1,2-diyl, prop-2-en-1,2-diyl, prop-1-en-1,3-diyl, cycloprop-1-en-1,2-diyl, cycloprop-2-en-1,2-diyl, cycloprop-2-en-1,1-diyl, prop-1-yn-1,3-diyl, etc.; butyldiyls such as, butan-1,1-diyl, butan-1,2-diyl, butan-1,3-diyl, butan-1,4-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 2-methyl-propan-1,2-diyl, cyclobutan-1,1-diyl; cyclobutan-1,2-diyl, cyclobutan-1,3-diyl, but-1-en-1,1-diyl, but-1-en-1,2-diyl, but-1-en-1,3-diyl, but-1-en-1,4-diyl, 2-methyl-prop-1-en-1,1-diyl, 2-methanylidene-propan-1,1-diyl, buta-1,3-dien-1,1-diyl,

buta-1,3-dien-1,2-diyl, buta-1,3-dien-1,3-diyl, buta-1,3-dien-1,4-diyl, cyclobut-1-en-1,2-diyl, cyclobut-1-en-1,3-diyl, cyclobut-2-en-1,2-diyl, cyclobuta-1,3-dien-1,2-diyl, cyclobuta-1,3-dien-1,3-diyl, but-1-yn-1,3-diyl, but-1-yn-1,4-diyl, buta-1,3-diyn-1,4-diyl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkanyldiyl, alkenyldiyl and/or alkynyldiyl is used. Where it is specifically intended that the two valencies are on the same carbon atom, the nomenclature "alkylidene" is used. In preferred embodiments, the alkyldiyl group is (C1-C6) alkyldiyl. Also preferred are saturated acyclic alkanyldiyl groups in which the radical centers are at the terminal carbons, *e.g.*, methandiyl (methano); ethan-1,2-diyl (ethano); propan-1,3-diyl (propano); butan-1,4-diyl (butano); and the like (also referred to as alkylenos, defined *infra*).

"Alkyleno" by itself or as part of another substituent refers to a straight-chain saturated or unsaturated alkyldiyl group having two terminal monovalent radical centers derived by the removal of one hydrogen atom from each of the two terminal carbon atoms of straight-chain parent alkane, alkene or alkyne. The locant of a double bond or triple bond, if present, in a particular alkyleno is indicated in square brackets. Typical alkyleno groups include, but are not limited to, methano; ethylenos such as ethano, etheno, ethyno; propylenos such as propano, prop[1]eno, propa[1,2]dieno, prop[1]yno, etc.; butylenos such as butano, but[1]eno, but[2]eno, buta[1,3]dieno, but[1]yno, but[2]yno, buta[1,3]diyno, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkano, alkeno and/or alkyno is used. In preferred embodiments, the alkyleno group is (C1-C6) or (C1-C3) alkyleno. Also preferred are straight-chain saturated alkano groups, *e.g.*, methano, ethano, propano, butano, and the like.

"Heteroalkyl," Heteroalkanyl," Heteroalkenyl," Heteroalkynyl," Heteroalkyldiyl" and "Heteroalkyleno" by themselves or as part of another substituent refer to alkyl, alkanyl, alkenyl, alkynyl, alkyldiyl and alkyleno groups, respectively, in which one or more of the carbon atoms are each independently replaced with the same or different heteratoms or heteroatomic groups. Typical heteroatoms and/or heteroatomic groups which can replace the carbon atoms include, but are not limited to, -O-, -S-, -S-O-, -NR'-, -PH-, -S(O)-, $-S(O)_2-$, -S(O) NR'-, $-S(O)_2NR'-$, and the like, including combinations thereof, where each R' is independently hydrogen or (C1-C6) alkyl.

"Cycloalkyl" and "Heterocycloalkyl" by themselves or as part of another substituent refer to cyclic versions of "alkyl" and "heteroalkyl" groups, respectively. For heteroalkyl groups, a heteroatom can occupy the position that is attached to the remainder of the

molecule. Typical cycloalkyl groups include, but are not limited to, cyclopropyl; cyelobutyls such as cyclobutanyl and cyclobutenyl; cyclopentyls such as cyclopentanyl and cyclopentenyl; cyclohexyls such as cyclohexanyl and cyclohexenyl; and the like. Typical heterocycloalkyl groups include, but are not limited to, tetrahydrofuranyl (*e.g.*, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, etc.), piperidinyl (*e.g.*, piperidin-1-yl, piperidin-2-yl, etc.), morpholinyl (*e.g.*, morpholin-3-yl, morpholin-4-yl, etc.), piperazinyl (*e.g.*, piperazin-1-yl, piperazin-2-yl, etc.), and the like.

"Acyclic Heteroatomic Bridge" refers to a divalent bridge in which the backbone atoms are exclusively heteroatoms and/or heteroatomic groups. Typical acyclic heteroatomic bridges include, but are not limited to, -O-, -S-, -S-O-, -NR'-, -PH-, -S(O)-, $-S(O)_2-$, -S(O) NR'-, $-S(O)_2NR'-$, and the like, including combinations thereof, where each R' is independently hydrogen or (C1-C6) alkyl.

"Parent Aromatic Ring System" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, tetrahydronaphthalene, etc. Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, tetrahydronaphthalene, triphenylene, trinaphthalene, and the like, as well as the various hydro isomers thereof.

"Aryl" by itself or as part of another substituent refers to a monovalent aromatic hydrocarbon group having the stated number of carbon atoms (*i.e.*, C5-C15 means from 5 to 15 carbon atoms) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene,

trinaphthalene, and the like, as well as the various hydro isomers thereof. In preferred embodiments, the aryl group is (C5-C15) aryl, with (C5-C10) being even more preferred. Particularly preferred aryls are cyclopentadienyl, phenyl and naphthyl.

"Arylaryl" by itself or as part of another substituent refers to a monovalent hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a ring system in which two or more identical or non-identical parent aromatic ring systems are joined directly together by a single bond, where the number of such direct ring junctions is one less than the number of parent aromatic ring systems involved. Typical arylaryl groups include, but are not limited to, biphenyl, triphenyl, phenyl-naphthyl, binaphthyl, biphenyl-naphthyl, and the like. Where the number of carbon atoms in an arylaryl group are specified, the numbers refer to the carbon atoms comprising each parent aromatic ring. For example, (C5-C15) arylaryl is an arylaryl group in which each aromatic ring comprises from 5 to 15 carbons, *e.g.*, biphenyl, triphenyl, binaphthyl, phenylnaphthyl, etc. Preferably, each parent aromatic ring system of an arylaryl group is independently a (C5-C15) aromatic, more preferably a (C5-C10) aromatic. Also preferred are arylaryl groups in which all of the parent aromatic ring systems are identical, *e.g.*, biphenyl, triphenyl, binaphthyl, trinaphthyl, etc.

"Biaryl" by itself or as part of another substituent refers to an arylaryl group having two identical parent aromatic systems joined directly together by a single bond. Typical biaryl groups include, but are not limited to, biphenyl, binaphthyl, bianthracyl, and the like. Preferably, the aromatic ring systems are (C5-C15) aromatic rings, more preferably (C5-C10) aromatic rings. A particularly preferred biaryl group is biphenyl.

"Arylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylakenyl and/or arylalkynyl is used. In preferred embodiments, the arylalkyl group is (C6-C21) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C1-C6) and the aryl moiety is (C5-C15). In particularly preferred embodiments the arylalkyl group is (C6-C13), *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C1-C3) and the aryl moiety is (C5-C10).

"Parent Heteroaromatic Ring System" refers to a parent aromatic ring system in which one or more carbon atoms are each independently replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups to replace the carbon atoms include, but are not limited to, N, NH, P, O, S, S(O), $S(O)_2$, Si, etc. Specifically included within the definition of "parent heteroaromatic ring systems" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, etc. Also included in the definition of "parent heteroaromatic ring system" are those recognized rings that include common substituents, such as, for example, benzopyrone and 1-methyl-1,2,3,4-tetrazole. Specifically excluded from the definition of "parent heteroaromatic ring system" are benzene rings fused to cyclic polyalkylene glycols such as cyclic polyethylene glycols. Typical parent heteroaromatic ring systems include, but are not limited to, acridine, benzimidazole, benzisoxazole, benzodioxan, benzodioxole, benzofuran, benzopyrone, benzothiadiazole, benzothiazole, benzotriazole, benzoxaxine, benzoxazole, benzoxazoline, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like.

"Heteroaryl" by itself or as part of another substituent refers to a monovalent heteroaromatic group having the stated number of ring atoms (*e.g.*, "5-14 membered" means from 5 to 14 ring atoms) derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, benzimidazole, benzisoxazole, benzodioxan, benzodiaxole, benzofuran, benzopyrone, benzothiadiazole, benzothiazole, benzotriazole, benzoxazine, benzoxazole, benzoxazoline, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole,

thiophene, triazole, xanthene, and the like, as well as the various hydro isomers thereof. In preferred embodiments, the heteroaryl group is a 5-14 membered heteroaryl, with 5-10 membered heteroaryl being particularly preferred.

"Heteroaryl-Heteroaryl" by itself or as part of another substituent refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a ring system in which two or more identical or non-identical parent heteroaromatic ring systems are joined directly together by a single bond, where the number of such direct ring junctions is one less than the number of parent heteroaromatic ring systems involved. Typical heteroaryl-heteroaryl groups include, but are not limited to, bipyridyl, tripyridyl, pyridylpurinyl, bipurinyl, etc. Where the number of atoms are specified, the numbers refer to the number of atoms comprising each parent heteroaromatic ring systems. For example, 5-15 membered heteroaryl-heteroaryl is a heteroaryl-heteroaryl group in which each parent heteroaromatic ring system comprises from 5 to 15 atoms, *e.g.*, bipyridyl, tripuridyl, etc. Preferably, each parent heteroaromatic ring system is independently a 5-15 membered heteroaromatic, more preferably a 5-10 membered heteroaromatic. Also preferred are heteroaryl-heteroaryl groups in which all of the parent heteroaromatic ring systems are identical.

"Biheteroaryl" by itself or as part of another substituent refers to a heteroaryl-heteroaryl group having two identical parent heteroaromatic ring systems joined directly together by a single bond. Typical biheteroaryl groups include, but are not limited to, bipyridyl, bipurinyl, biquinolinyl, and the like. Preferably, the heteroaromatic ring systems are 5-15 membered heteroaromatic rings, more preferably 5-10 membered heteroaromatic rings.

"Heteroarylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylakenyl and/or heteroarylalkynyl is used. In preferred embodiments, the heteroarylalkyl group is a 6-21 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is (C1-C6) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In particularly preferred embodiments, the heteroarylalkyl is a 6-13 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety is (C1-C3) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

"Halogen" or "Halo" by themselves or as part of another substituent, unless otherwise stated, refer to fluoro, chloro, bromo and iodo.

"Haloalkyl" by itself or as part of another substituent refers to an alkyl group in which one or more of the hydrogen atoms is replaced with a halogen. Thus, the term "haloalkyl" is meant to include monohaloalkyls, dihaloalkyls, trihaloalkyls, etc. up to perhaloalkyls. For example, the expression "(C1-C2) haloalkyl" includes fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, perfluoroethyl, etc.

The above-defined groups may include prefixes and/or suffixes that are commonly used in the art to create additional well-recognized substituent groups. As examples, "alkyloxy" or "alkoxy" refers to a group of the formula -OR", "alkylamine" refers to a group of the formula –NHR" and "dialkylamine" refers to a group of the formula –NR"R", where each R" is independently an alkyl. As another example, "haloalkoxy" or "haloalkyloxy" refers to a group of the formula –OR''', where R''' is a haloalkyl.

"Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison *et al.*, *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (*e.g.*, TMS or TIPPS groups) and allyl ethers.

"Prodrug" refers to a derivative of an active 2,4-pyrimidinediamine compound (drug) that requires a transformation under the conditions of use, such as within the body, to release the active 2,4-pyrimidinediamine drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs are typically obtained by masking a functional group in the 2,4-pyrimidinediamine drug believed to be in part required for activity with a progroup (defined below) to form a promoiety which

undergoes a transformation, such as cleavage, under the specified conditions of use to release the functional group, and hence the active 2,4-pyrimidinediamine drug. The cleavage of the promoiety may proceed spontaneously, such as by way of a hydrolysis reaction, or it may be catalyzed or induced by another agent, such as by an enzyme, by light, by aeid or base, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature. The agent may be endogenous to the conditions of use, such as an enzyme present in the cells to which the prodrug is administered or the acidic conditions of the stomach, or it may be supplied exogenously.

A wide variety of progroups, as well as the resultant promoieties, suitable for masking functional groups in the active 2,4-pyrimidinediamines compounds to yield prodrugs are well-known in the art. For example, a hydroxyl functional group may be masked as a sulfonate, ester or carbonate promoiety, which may be hydrolyzed *in vivo* to provide the hydroxyl group. An amino functional group may be masked as an amide, carbamate, imine, urea, phosphenyl, phosphoryl or sulfenyl promoiety, which may be hydrolyzed *in vivo* to provide the amino group. A carboxyl group may be masked as an ester (including silyl esters and thioesters), amide or hydrazide promoiety, which may be hydrolyzed *in vivo* to provide the carboxyl group. Other specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art.

"Progroup" refers to a type of protecting group that, when used to mask a functional group within an active 2,4-pyrimidinediamine drug to form a promoiety, converts the drug into a prodrug. Progroups are typically attached to the functional group of the drug *via* bonds that are cleavable under specified conditions of use. Thus, a progroup is that portion of a promoiety that cleaves to release the functional group under the specified conditions of use. As a specific example, an amide promoiety of the formula $-NH-C(O)CH_3$ comprises the progroup $-C(O)CH_3$.

"Fc Receptor" refers to a member of the family of cell surface molecules that binds the Fc portion (containing the specific constant region) of an immunoglobulin. Each Fc receptor binds immunoglobulins of a specific type. For example the Fcα receptor ("FcαR") binds IgA, the FcϵR binds IgE and the FcγR binds IgG.

The FcαR family includes the polymeric Ig receptor involved in epithelial transport of IgA/IgM, the mycloid specific receptor RcαRI (also called CD89), the Fcα/μR and at least two alternative IgA receptors (for a recent review see Monteiro & van de Winkel, 2003, Annu. Rev. Immunol, advanced e-publication. The FcαRI is expressed on neutrophils, eosinophils, moncytes/macrophages, dendritic cells and kupfer cells. The

FcαRI inclues one alpha chain and the FcR gamma homodimer that bears an activation motif (ITAM) in the cytoplasmic domain and phosphorylates Syk kinase.

The FcεR family includes two types, designated FcεRI and FcεRII (also known as CD23). FcεRI is a high affinity receptor (binds IgE with an affinity of about $10^{10}M^{-1}$) found on mast, basophil and eosinophil cells that anchors monomeric IgE to the cell surface. The FcεRI possesses one alpha chain, one beta chain and the gamma chain homodimer discussed above. The FcεRII is a low affinity receptor expressed on mononuclear phagocytes, B lymphocytes, eosinophils and platelets. The FcεRII comprises a single polypeptide chain and does not include the gamma chain homodimer.

The FcγR family includes three types, designated FcγRI (also known as CD64), FcγRII (also known as CD32) and FcγRIII (also known as CD16). FcγRI is a high affinity receptor (binds IgG1 with an affinity of $10^{8}M^{-1}$) found on mast, basophil, mononuclear, neutrophil, eosinophil, deudritic and phagocyte cells that anchors nomomeric IgG to the cell surface. The FcγRI includes one alpha chain and the gamma chain dimer shared by FcαRI and FcεRI.

The FcγRII is a low affinity receptor exprcssed on neutrophils, monocytes, eosinophils, platelets and B lymphocytes. The FcγRII includes one alpha chain, and does not include the gamma chain homodimer discussed above.

The FcγRIII is a low affinity (bindes IgG1 with an affinity of $5x10^{5}M^{-1}$) expressed on NK, eosinophil, macrophage, neutrophil and mast cells. It comprises one alpha chain and the gamma homodimer shared by FcαRI, FcεRI and FcγRI.

Skilled artisans will recognize that the subunit structure and binding properties of these various Fc receptors, cell types expressing them, are not completely characterized. The above discussion merely reflects the current state-of-the-art regarding these receptors (*see, e.g.,* Immunobiology: The Immune System in Health & Disease, 5th Edition, Janeway et al., Eds, 2001, ISBN 0-8153-3642-x, Figure 9.30 at pp. 371), and is not intended to be limiting with respect to the myriad receptor signaling cascades that can be regulated with the compounds described herein.

"Fc Receptor-Mediated Degranulation" or "Fc Receptor-Induced Degranulation" refers to degranulation that proceeds *via* an Fc receptor signal transduction cascade initiated by crosslinking of an Fc receptor.

"IgE-Induced Degranulation" or "FcεRI-Mediated Degranulation" refers to degranulation that proceeds *via* the IgE receptor signal transduction cascade initiated by

crosslinking of FcεR1-bound IgE. The crosslinking may be induced by an IgE-specific allergen or other multivalent binding agent, such as an anti-IgE antibody. Referring to FIG. 2, in mast and/or basophil cells, the FcεRI signaling cascade leading to degranulation may be broken into two stages: upstream and downstream. The upstream stage includes all of the processes that occur prior to calcium ion mobilization (illustrated as "Ca^{2+}" in FIG. 2; see also FIG. 3). The downstream stage includes calcium ion mobilization and all processes downstream thereof. Compounds that inhibit FcεRI-mediated degranulation may act at any point along the FcεRI-mediated signal transduction cascade. Compounds that selectively inhibit upstream FcεRI-mediated degranulation act to inhibit that portion of the FcεRI signaling cascade upstream of the point at which calcium ion mobilization is induced. In cell-based assays, compounds that selectively inhibit upstream FcεRI-mediated degranulation inhibit degranulation of cells such as mast or basophil cells that are activated or stimulated with an IgE-specific allergen or binding agent (such as an anti-IgE antibody) but do not appreciably inhibit degranulation of cells that are activated or stimulated with degranulating agents that bypass the FcεRI signaling pathway, such as, for example the calcium ionophores ionomycin and A23187.

"IgG-Induced Degranulation" or "FcγRI-Mediated Degranulation" refers to degranulation that proceeds *via* the FcγRI signal transduction cascade initiated by crosslinking of FcγRI-bound IgG. The crosslinking may be induced by an IgG-specific allergen or another multivalent binding agent, such as an anti-IgG or fragment antibody. Like the FcεRI signaling cascade, in mast and basophil cells the FcγRI signaling cascade also leads to degranulation which may be broken into the same two stages: upstream and downstream. Similar to FcεRI-mediated degranulation, compounds that selectively inhibit upstream FcγRI-mediated degranulation act upstream of the point at which calcium ion mobilization is induced. In cell-based assays, compounds that selectively inhibit upstream FcγRI-mediated degranulation inhibit degranulation of cells such as mast or basophil cells that are activated or stimulated with an IgG-specific allergen or binding agent (such as an anti-IgG antibody or fragment) but do not appreciably inhibit degranulation of cells that are activated or stimulated with degranulating agents that bypass the FcγRI signaling pathway, such as, for example the calcium ionophores ionomycin and A23187.

"Ionophore-Induced Degranulation" or "Ionophore-Mediated Degranulation" refers to degranulation of a cell, such as a mast or basophil cell, that occurs upon exposure to a calcium ionophore such as, for example, ionomycin or A23187.

"Syk Kinsase" refers to the well-known 72kDa non-receptor (cytoplasmic) spleen protein tyrosine kinase expressed in B-cells and other hematopoetic cells. Syk kinase includes two consensus Src-homology 2 (SH2) domains in tandem that bind to phosphorylated immunoreceptor tyrosine-based activation motifs ("ITAMs"), a "linker" domain and a catalytic domain (for a review of the structure and function of Syk kinase see Sada *et al.*, 2001, J. Biochem. (Tokyo) 130:177-186); see also Turner *et al.*, 2000, Immunology Today 21:148-154). Syk kinase has been extensively studied as an effector of B-cell receptor (BCR) signaling (Turner *et al.*, 2000, *supra*). Syk kinase is also critical for tyrosine phosphorylation of multiple proteins which regulate important pathways leading from immunoreceptors, such as Ca^{2+} mobilization and mitogen-activated protein kinase (MAPK) cascades (see, e.g., FIG. 2) and degranulation. Syk kinase also plays a critical role in integrin signaling in neutrophils (*see, e.g.*, Mocsai *et al.* 2002, Immunity 16:547-558).

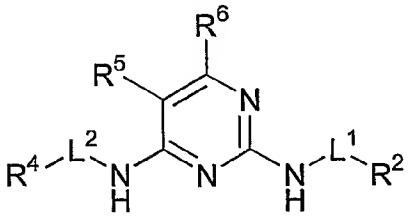
As used herein, Syk kinase includes kinases from any species of animal, including but not limited to, homosapiens, simian, bovine, porcine, rodent, etc., recognized as belonging to the Syk family. Specifically included are isoforms, splice variants, allelic variants, mutants, both naturally occuring and man-made. The amino acid sequences of such Syk kinases are well known and available from GENBANK. Specific examples of mRNAs encoding different isoforms of human Syk kinase can be found at GENBANK accession no. gi|21361552|ref|NM__003177.2|, gi|496899|emb|Z29630.1|HSSYKPTK[496899] and gi|15030258|gb|BC011399.1|BC011399[15030258], which are incorporated herein by reference.

Skilled artisans will appreciate that tyrosine kinases belonging to other families may have active sites or binding pockets that are similar in three-dimensional structure to that of Syk. As a consequence of this structural similarity, such kinases, referred to herein as "Syk mimics," are expected to catalyze phosphorylation of substrates phosphorylated by Syk. Thus, it will be appreciated that such Syk mimics, signal transduction cascades in which such Syk mimics play a role and biological responses effected by such Syk mimics and Syk mimic-dependent signaling cascades may be regulated, and in particular inhibited, with the 2,4-pyrimidinediamine compounds described herein.

"Syk-Dependent Signaling Cascade" refers to a signal transduction cascade in which Syk kinase plays a role. Non-limiting examples of such Syk-dependent signaling cascades include the FcαRI, FcεRI, FcγRI, FcγRIII, BCR and integrin signaling cascades.

6.2 The 2,4-Pyrimidinediamine Compounds

The compounds of the invention are generally 2,4-pyrimidinediamine compounds according to structural formula (I):



including salts, hydrates, solvates and N-oxides thereof, wherein:

L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond and a linker;

R^2 is selected from the group consisting of (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^4 is selected from the group consisting of hydrogen, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C3-C8) cycloalkyl optionally substituted with one or more of the same or different R^8 groups, cyclohexyl optionally substituted with one or more of the same or different R^8 groups, 3-8 membered cycloheteroalkyl optionally substituted with one or more of the same or different R^8 groups, (C5-C15) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups and 5-15 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups;

R^5 is selected from the group consisting of R^6, (C1-C6) alkyl optionally substituted with one or more of the same or different R^8 groups, (C1-C4) alkanyl optionally substituted with one or more of the same or different R^8 groups, (C2-C4) alkenyl optionally substituted with one or more of the same or different R^8 groups and (C2-C4) alkynyl optionally substituted with one or more of the same or different R^8 groups;

each R^6 is independently selected from the group consisting of hydrogen, an electronegative group, $-OR^d$, $-SR^d$, (C1-C3) haloalkyloxy, (C1-C3) perhaloalkyloxy, $-NR^cR^c$, halogen, (C1-C3) haloalkyl,(C1-C3) perhaloalkyl, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-OC(O)R^d$, $-SC(O)R^d$, $-OC(O)OR^d$, $-SC(O)OR^d$, $-OC(O)NR^cR^c$, $-SC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-SC(NH)NR^cR^c$, $-[NHC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$ and $-[NHC(NH)]_nNR^cR^c$, (C5-C10) aryl optionally substituted with one or more of the same or different R^8 groups, phenyl optionally substituted with one or more of the same or different R^8 groups, (C6-C16) arylalkyl optionally substituted with one or more of the same or different R^8 groups, 5-10 membered heteroaryl optionally substituted with one or more of the same or different R^8 groups and 6-16 membered heteroarylalkyl optionally substituted with one or more of the same or different R^8 groups;

R^8 is selected from the group consisting of R^a, R^b, R^a substituted with one or more of the same or different R^a or R^b, $-OR^a$ substituted with one or more of the same or different R^a or R^b, $-B(OR^a)_2$, $-B(NR^cR^c)_2$, $-(CH_2)_m-R^b$, $-(CHR^a)_m-R^b$, $-O-(CH_2)_m-R^b$, $-S-(CH_2)_m-R^b$, $-O-CHR^aR^b$, $-O-CR^a(R^b)_2$, $-O-(CHR^a)_m-R^b$, $-O-(CH_2)_m-CH[(CH_2)_mR^b]R^b$, $-S-(CHR^a)_m-R^b$, $-C(O)NH-(CH_2)_m-R^b$, $-C(O)NH-(CHR^a)_m-R^b$, $-O-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-S-(CH_2)_m-C(O)NH-(CH_2)_m-R^b$, $-O-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-S-(CHR^a)_m-C(O)NH-(CHR^a)_m-R^b$, $-NH-(CH_2)_m-R^b$, $-NH-(CHR^a)_m-R^b$, $-NH[(CH_2)_mR^b]$, $-N[(CH_2)_mR^b]_2$, $-NH-C(O)-NH-(CH_2)_m-R^b$, $-NH-C(O)-(CH_2)_m-CHR^bR^b$ and $-NH-(CH_2)_m-C(O)-NH-(CH_2)_m-R^b$;

each R^a is independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C3-C8) cycloalkyl, cyclohexyl, (C4-C11) cycloalkylalkyl, (C5-C10) aryl, phenyl, (C6-C16) arylalkyl, benzyl, 2-6 membered heteroalkyl, 3-8 membered cycloheteroalkyl, morpholinyl, piperazinyl, homopiperazinyl, piperidinyl, 4-11 membered cycloheteroalkylalkyl, 5-10 membered heteroaryl and 6-16 membered heteroarylalkyl;

each R^b is a suitable group independently selected from the group consisting of =O, $-OR^d$, (C1-C3) haloalkyloxy, $-OCF_3$, =S, $-SR^d$, $=NR^d$, $=NOR^d$, $-NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^d$, $-S(O)_2R^d$, $-S(O)_2OR^d$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^d$, $-OS(O)_2R^d$, $-OS(O)_2OR^d$, $-OS(O)_2NR^cR^c$, $-C(O)R^d$, $-C(O)OR^d$, $-C(O)NR^cR^c$, $-C(NH)NR^cR^c$, $-C(NR^a)NR^cR^c$, $-C(NOH)R^a$, $-C(NOH)NR^cR^c$, $-OC(O)R^d$, $-OC(O)OR^d$, $-OC(O)NR^cR^c$, $-OC(NH)NR^cR^c$, $-OC(NR^a)NR^cR^c$, $-[NHC(O)]_nR^d$,

$-[NR^aC(O)]_nR^d$, $-[NHC(O)]_nOR^d$, $-[NR^aC(O)]_nOR^d$, $-[NHC(O)]_nNR^cR^c$, $-[NR^aC(O)]_nNR^cR^c$, $-[NHC(NH)]_nNR^cR^c$ and $-[NR^aC(NR^a)]_nNR^cR^c$;

each R^c is independently R^a, or, alternatively, each R^c is taken together with the nitrogen atom to which it is bonded to form a 5 to 8-membered cycloheteroalkyl or heteroaryl which may optionally include one or more of the same or different additional heteroatoms and which is optionally substituted with one or more of the same or different R^a or suitable R^b groups;

each R^d is independently R^a;

each *m* is independently an integer from 1 to 3; and

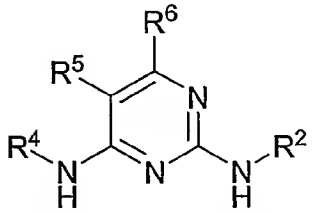
each *n* is independently an integer from 0 to 3.

In the compounds of structural formula (I), L^1 and L^2 represent, independently of one another, a direct bond or a linker. Thus, as will be appreciated by skilled artisans, the substituents R^2 and/or R^4 may be bonded either directly to their respective nitrogen atoms or, alternatively, spaced away from their respective nitrogen atoms by way of a linker. The identity of the linker is not critical and typical suitable linkers include, but are not limited to, (C1-C6) alkyldiyls, (C1-C6) alkanos and (C1-C6) heteroalkyldiyls, each of which may be optionally substituted with one or more of the same or different R^8 groups, where R^8 is as previously defined for structural formula (I). In a specific embodiment, L^1 and L^2 are each, independently of one another, selected from the group consisting of a direct bond, (C1-C3) alkyldiyl optionally substituted with one or more of the same or different R^a, suitable R^b or R^9 groups and 1-3 membered heteroalkyldiyl optionally substituted with one or more of the same or different R^a, suitable R^b or R^9 groups, wherein R^9 is selected from the group consisting of (C1-C3) alkyl, $-OR^a$, $-C(O)OR^a$, (C5-C10) aryl optionally substituted with one or more of the same or different halogens, phenyl optionally substituted with one or more of the same or different halogens, 5-10 membered heteroaryl optionally substituted with one or more of the same or different halogens and 6 membered heteroaryl optionally substituted with one or more of the same or different halogens; and R^a and R^b are as previously defined for structural formula (I). Specific R^9 groups that may be used to substitute L^1 and L^2 include $-OR^a$, $-C(O)OR^a$, phenyl, halophenyl and 4-halophenyl, wherein R^a is as previously defined for structural formula (I).

In another specific embodiment, L^1 and L^2 are each, independently of one another, selected from the group consisting of methano, ethano and propano, each of which may be optionally monosubstituted with an R^9 group, where R^9 is as previously defined above.

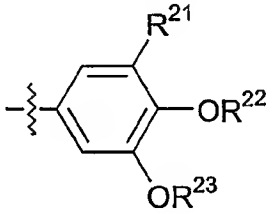
In all of the above embodiments, specific R^a groups that may be included in R^9 groups are selected from the group consisting of hydrogen, (C1-C6) alkyl, phenyl and benzyl.

In still another specific embodiment, L^1 and L^2 are each a direct bond such that the 2,4-pyrimidinediamine compounds of the invention are compounds according to structural formula (Ia):



including salts, hydrates, solvates and N-oxides thereof, wherein R^2, R^4, R^5 and R^6 are as previously defined for structural formula (I). Additional specific embodiments of the 2,4-pyrimidinediamine compounds of the invention are described below.

In a first embodiment of the compounds of structural formulae (I) and (Ia), R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for their respective structures (I) and (Ia), with the proviso that R^2 is not 3,4,5-trimethoxyphenyl, 3,4,5-tri (C1-C6) alkoxyphenyl or

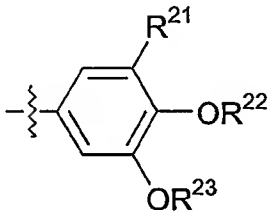


where R^{21}, R^{22} and R^{23} are as defined for R^1, R^2 and R^3, respectively of U.S. Patent No. 6,235,746, the disclosure of which is incorporated by reference. In a specific embodiment of this first embodiment, R^{21} is hydrogen, halo, straight-chain or branched (C1-C6) alkyl optionally substituted with one or more of the same or different R^{25} groups, hydroxyl, (C1-C6) alkoxy optionally substituted with one or more of the same or different phenyl or R^{25} groups, thiol (-SH), (C1-C6) alkylthio optionally substituted with one or more of the same or different phenyl or R^{25} groups, amino ($-NH_2$), $-NHR^{26}$ or $-NR^{26}R^{26}$; R^{22} and R^{23} are each, independently of one another, a (C1-C6) straight-chain or branched alkyl optionally substituted with one or more of the same or different R^{25} groups; R^{25} is selected from the group consisting of halo, hydroxyl, (C1-C6) alkoxy, thiol, (C1-C6) alkylthio, (C1-C6) alkylamino and (C1-C6) dialkylamino; and each R^{26} is independently a (C1-C6) alkyl optionally substituted with one or more of the same or different phenyl or R^{25} groups or a

-C(O)R^{27}, where R^{27} is a (C1-C6) alkyl optionally substituted with one or more of the same or different phenyl or R^{25} groups.

In another specific embodiment of this first embodiment, R^{21} is methoxy optionally substituted with one or more of the same or different halo groups and/or R^{22} and R^{23} are each, independently of one another, a methyl or ethyl optionally substituted with one or more of the same or different halo groups.

In a second embodiment of the compounds of structural formulae (I) and (Ia), R^2, R^4, R^5 and L^2 are as previously described for their respective structures (I) and (Ia), L^1 is a direct bond and R^6 is hydrogen, with the proviso that R^2 is not 3,4,5-trimethoxyphenyl, 3,4,5-tri (C1-C6) alkoxyphenyl or



where R^{21}, R^{22} and R^{23} are as defined above, in connection with the first embodiment.

In a third embodiment, the 2,4-pyrimidinediamine compounds of structural formulae (I) and (Ia) exclude one or more of the following compounds:

N2,N4-bis(4-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R070790);

N2,N4-bis(2-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R081166);

N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R088814);

N2,N4-bis(2-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R088815);

N2,N4-bisphenyl-5-fluoro-2,4-pyrimidinediamine (R091880);

N2,N4-bis(3-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R092788);

N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R067962);

N2,N4-bis(2,5-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067963);

N2,N4-bis(3,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R067964);

N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R0707153);

N2,N4-bis(2,4-dimethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R070791);

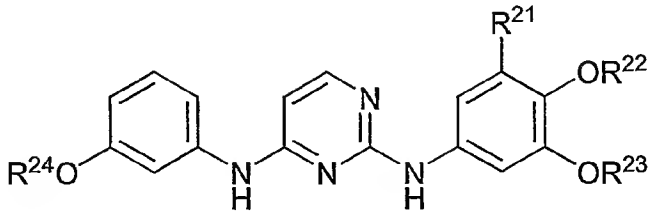
N2,N4-bis(3-bromophenyl)-5-fluoro-2,4-pyrimidinediamine (R008958);

N2,N4-bis(phenyl)-5-fluoro-2,4-pyrimidinediamine;

N2,N4-bis(morpholino)-5-fluoro-2,4-pyrimidinediamine; and

N2,N4-bis[(3-chloro-4-methoxyphenyl)]-5-fluoro-2,4-pyrimidinediamine.

In a fourth embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds according to the following structural formula (Ib):



wherein R^{24} is (C1-C6) alkyl; and R^{21}, R^{22} and R^{23} are as previously defined in connection with the first embodiment.

In a fifth embodiment, the compounds of structural formulae (I) and (Ia) exclude the compounds described in Examples 1-141 of U.S. Patent No. 6,235,746, the disclosure of which is incorporated herein by reference.

In a sixth embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds defined by formula (1) or formula 1(a) of this U.S. Patent No. 6,235,746 (see, e.g., the disclosure at Col. 1, line 48 through Col. 7, line 49 and Col. 8, lines 9-36, which is incorporated by reference).

In a seventh embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds in which R^5 is cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl, when R^2 is a substituted phenyl; R4 is a substituted or unsubstituted (C1-C6) alkyl, (C_3-C_8) cycloalkyl, 3-8 membered cycloheteralkyl or 5-15 membered heteroaryl; and R^6 is hydrogen.

In an eighth embodiment, the compounds of structural formulae (I) and (Ia) exclude the compounds defined by formulae (I) and (X) of WO 02/04429 or any compound disclosed in WO 02/04429, the disclosure of which is incorporated herein by reference.

In a ninth embodiment of the compounds of structural formulae (I) and (Ia), when R^5 is cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl; and R^6 is hydrogen, then R^2 is other than a substituted phenyl group.

In a tenth embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds in which R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole ring which is attached to the remainder of the molecule *via* its ring nitrogen atom.

In an eleventh embodiment, the compounds of structural formulae (I) and (Ia) exclude compounds defined by formulae (I) and (IV) of U.S. Patent No. 4,983,608 or any

compound disclosed in U.S. Patent No. 4,983,608, the disclosure of which is incorporated herein by reference.

Those of skill in the art will appreciate that in the compounds of formulae (I) and (Ia), R^2 and R^4 may be the same or different, and may vary broadly. When R^2 and/or R^4 are optionally substituted rings, such as optionally substituted cycloalkyls, cycloheteroalkyls, aryls and heteroaryls, the ring may be attached to the remainder of the molecule through any available carbon or heteroatom. The optional substituents may be attached to any available carbon atoms and/or heteroatoms.

In a twelfth embodiment of the compounds of structural formulae (I) and (Ia), R^2 and/or R^4 is an optionally substituted phenyl or an optionally substituted (C5-C15) aryl, subject to the provisos that (1) when R^6 is hydrogen, then R^2 is not 3,4,5-trimethoxyphenyl or 3,4,5-tri (C1-C6) alkoxyphenyl; (2) when R^2 is a 3,4,5-trisubstituted phenyl, then the substituents at the 3- and 4-positions are not simultaneously methoxy or (C1-C6) alkoxy; or (3) when R^6 is hydrogen and R^4 is (C1-C6) alkyl, (C_3-C_8) cycloalkyl, 3-8 membered cycloheteroalkyl or 5-15 membered heteroaryl, then R^5 is other than cyano. Alternatively, R^2 is subject to the provisos described in connection with the first or second embodiments. The optionally substituted aryl or phenyl group may be attached to the remainder of the molecule through any available carbon atom. Specific examples of optionally substituted phenyls include phenyls that are optionally mono-, di- or tri-substituted with the same or different R^8 groups, where R^8 is as previously defined for structural formula (I) and subject to the above provisos. When the phenyl is mono-substituted, the R^8 substituent may be positioned at either the *ortho, meta* or *para* position. When positioned at the *ortho, meta* or *para* position, R^8 is preferably selected from the group consisting of (C1-C10) alkyl, (C1-C10) branched alkyl, $-OR^a$ optionally substituted with one or more of the same or different R^b groups, $-O-C(O)OR^a$, $-O-(CH_2)_m-C(O)OR^a$, $-C(O)OR^a$, $-O-(CH_2)_m-NR^cR^c$, $-O-C(O)NR^cR^c$, $-O-(CH_2)_m-C(O)NR^cR^c$, $-O-C(NH)NR^cR^c$, $-O-(CH_2)_m-C(NH)NR^cR^c$ and $-NH-(CH_2)_m-NR^cR^c$, where *m*, R^a and R^c are as previously defined for structural formula (I). In one embodiment of these compounds, $-NR^cR^c$ is a 5-6 membered heteroaryl which optionally includes one or more of the same or different additional heteroatoms. Specific examples of such 5-6 membered heteroaryls include, but are not limited to, oxadiazolyl, triazolyl, thiazolyl, oxazolyl, tetrazolyl and isoxazolyl.

In another embodiment of these compounds, $-NR^cR^c$ is a 5-6 membered saturated cycloheteroalkyl ring which optionally includes one or more of the same or different

heteroatoms. Specific examples of such cycloheteroalkyls include, but are not limited to, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl and morpholinyl.

In still another embodiment of these compounds, each R^a is independently a (C1-C6) alkyl and/or each $-NR^cR^c$ is $-NHR^a$, where R^a is a (C1-C6) alkyl. In one specific embodiment, R^8 is $-O-CH_2-C(O)NHCH_3$. In another specific embodiment R^8 is –OH.

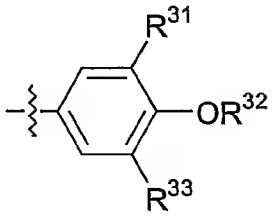
When the phenyl is di-substituted or tri-substituted, the R^8 substituents may be positioned at any combination of positions. For example, the R^8 substituents may be positioned at the 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, 2,5,6- or 3,4,5-positions. In one embodiment of compounds including a disubstituted phenyl, the substituents are positioned other than 3,4. In another embodiment they are positioned 3,4. In one embodiment of compounds including a trisubstituted phenyl, the substituents are positioned other than 3,4,5 or, alternatively, no two of the substituents are positioned 3,4. In another embodiment, the substituents are positioned 3,4,5.

Specific examples of R^8 substituents in such di- and trisubstituted phenyls include the various R^8 substituents described above in connection with the *ortho, meta* and *para* substituted phenyls.

In another specific embodiment, R^8 substituents useful for substitituting such di-and trisubstituted phenyls include (C1-C6) alkyl, (C1-C6) alkoxy, methoxy, halo, chloro, (C1-C6) perhaloalkyl, $-CF_3$, (C1-C6) perhaloalkoxy and $-OCF_3$. In a preferred embodiment, such R^8 substituents are positioned 3,4 or 3,5. Specific examples of preferred di-substituted phenyl rings include 3-chloro-4-methoxy-phenyl, 3-methoxy-4-chlorophenyl, 3-chloro-4-trifluoromethoxy-phenyl, 3-trifluoromethoxy-4-chloro-phenyl, 3,4-dichloro-phenyl, 3,4-dimethoxyphenyl and 3,5-dimethoxyphenyl, with the provisos that: (1) when R^4 is one of the above-identified phenyls, and R^5 and R^6 are each hydrogen, then R^2 is not 3,4,5-tri(C1-C6)alkoxyphenyl or 3,4,5-trimethoxyphenyl; (2) when R^2 is 3,4-dimethoxyphenyl and R^5 and R^6 are each hydrogen, then R4 is not 3-(C1-C6)alkoxyphenyl, 3-methoxyphenyl, 3,4-di-(C1-C6) alkoxyphenyl or 3,4-dimethoxyphenyl; (3) when R^4 is 3-chloro-4-methoxyphenyl and R^5 is halo or fluoro, and optionally R^6 is hydrogen, then R^2 is not 3-chloro-4-(C1-C6)alkoxyphenyl or 3-ehloro-4-methoxyphenyl; (4) when R^4 is 3,4-dichlorophenyl, R^5 is hydrogen, (C1-C6) alkyl, methyl, halo or chloro and optionally R^6 is hydrogen, then R^2 is not a phenyl mono substituted at the *para* position with a (C1-C6) alkoxy group which is optionally substituted with one or more of the same or different R^b, -OH or $-NR^cR^c$ groups, where R^b and R^c are as

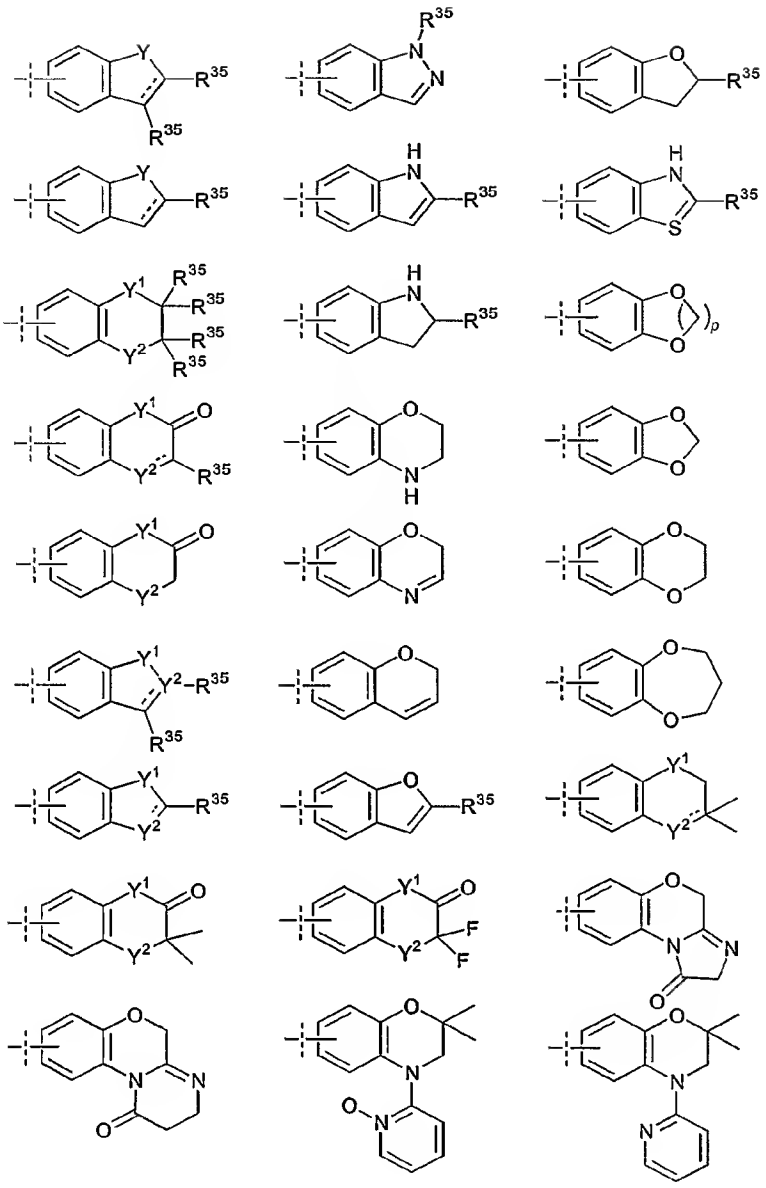
previously described for structural formula (I); and/or (5) R^2 and/or R^4 is not 3,4,5-tri(C1-C6)alkoxyphenyl or 3,4,5-trimethoxyphenyl, especially when R^5 and R^6 are each hydrogen..

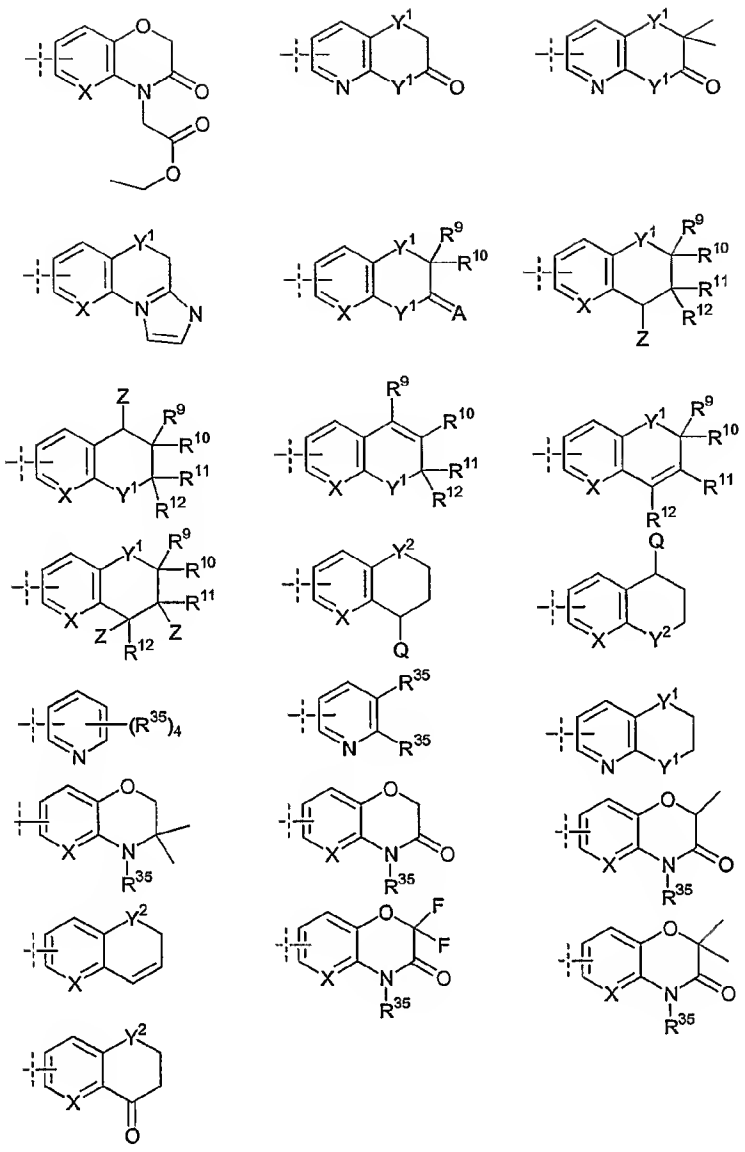
In another embodiment of compounds including a trisubstituted phenyl, the trisubstituted phenyl has the formula:



wherein: R^{31} is methyl or (C1-C6) alkyl; R^{32} is hydrogen, methyl or (C1-C6) alkyl; and R^{33} is a halo group.

In a thirteenth embodiment of the compounds of structural formulae (I) and (Ia), R^2 and/or R^4 is an optionally substituted heteroaryl. Typical heteroaryl groups according to this thirteenth embodiment comprise from 5 to 15, and more typically from 5 to 11 ring atoms, and include one, two, three or four of the same or different heteratoms or heteroatomic groups selected from the group consisting of N, NH, O, S, S(O) and $S(O)_2$. The optionally substituted heteroaryl may be attached to its respective C2 or C4 nitrogen atom or linker L^1 or L^2 through any available carbon atom or heteroatom, but is typically attached *via* a carbon atom. The optional substituents may be the same or different, and may be attached to any available carbon atom or heteroatom. In one embodiment of these compounds, R^5 is other than bromo, nitro, trifluoromethyl, cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl. In another embodiment of these compounds, when R^2 and R^4 are each a substituted or unsubstituted pyrrole or indole, then the ring is attached to the remainder of the molecule *via* a ring carbon atom. In still another embodiment of compounds including an optionally substituted heteroaryl group, the heteroaryl is unsubstituted or substituted with from one to four of the same or different R^8 groups, where R^8 is as previously defined for structural formula (I). Specific examples of such optionally substituted heteroaryls include, but are not limited to, the following heteroaryl groups:





wherein:

p is an integer from one to three;

each - - - independently represents a single bond or a double bond;

R^{35} is hydrogen or R^8, where R^8 is as previously defined for structural formula (I);

X is selected from the group consisting of CH, N and N-O;

each Y is independently selected from the group consisting of O, S and NH;

each Y^1 is independently selected from the group consisting of O, S, SO, SO_2, $SONR^{36}$, NH and NR^{37};

each Y^2 is independently selected from the group consisting of CH, CH_2, O, S, N, NH and NR^{37};

R^{36} is hydrogen or alkyl;

R^{37} is selected from the group consisting of hydrogen and a progroup, preferably hydrogen or a progroup selected from the group consisting of aryl, arylalkyl, heteroaryl, R^a, R^b–CR^aR^b-O-C(O)R^8, -CR^aR^b-O-PO(OR^8)$_2$, -CH_2-O-PO(OR^8)$_2$, -CH_2-PO(OR^8)$_2$, -C(O)-CR^aR^b-N(CH_3)$_2$, -CR^aR^b-O-C(O)-CR^aR^b-N(CH_3)$_2$, -C(O)R^8, -C(O)CF_3 and -C(O)-NR^8-C(O)R^8;

A is selected from the group consisting of O, NH and NR^{38};

R^{38} is selected from the group consisting of alkyl and aryl;

R^9, R^{10}, R^{11} and R^{12} are each, independently of one another, selected from the group consisting of alkyl, alkoxy, halogen, haloalkoxy, aminoalkyl and hydroxyalkyl, or, alternatively, $R^9$and R^{10} and/or R^{11} and R^{12} are taken together form a ketal;

each Z is selected from the group consisting of hydroxyl, alkoxy, aryloxy, ester, carbamate and sulfonyl;

Q is selected from the group consisting of -OH, OR^8, -NR^cR^c, -NHR^{39}-C(O)R^8, -NHR^{39}-C(O)OR^8, -NR^{39}-CHR^{40}-R^b, -NR^{39}-(CH_2)$_m$-R^b and -NR^{39}-C(O)-CHR^{40}-NR^cR^c;

R^{39} and R^{40} are each, independently of one another, selected from the group consisting of hydrogen, alkyl, aryl, alkylaryl;arylalkyl and NHR^8; and

R^a, R^b and R^c are as previously defined for structural formula (I). Preferred R^b substitutents for Q are selected from -C(O)OR^8, -O-C(O)R^8, -O-P(O)(OR^8)$_2$ and -P(O)(OR^8)$_2$.

In one embodiment of the above-depicted heteroaryls, as well as other 5-15 membered heteroaryls according to this embodiment of the invention, each R^8 is independently selected from the group consisting of R^d, -NR^cR^c, -(CH_2)$_m$-NR^cR^c, -C(O)NR^cR^c, -(CH_2)$_m$-C(O)NR^cR^c, -C(O)OR^d, -(CH_2)$_m$-C(O)OR^d and -(CH_2)$_m$-OR^d, where m, R^c and R^d are as previously defined for structural formula (I).

In a specific embodiment, R^d and/or R^c is selected from the group consisting of R^a and (C3-C8) cycloalkyl optionally substituted with one or more of the same or different hydroxyl, amino or carboxyl groups.

In another embodiment of the above-depicted heteroaryls, each R^{35} is hydrogen or (C1-C6) ethyl or methyl.

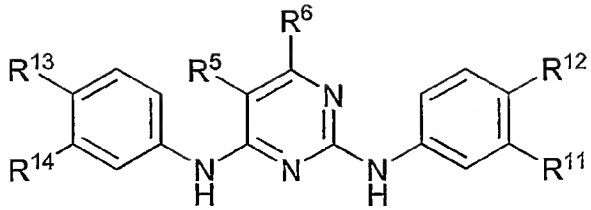
In still another embodiment of the above-depicted heteroaryls, the aromatic ring connectivity is either at the 5 or 6 position. It should be understood that either R^2 or R^4 can utilize the heteroaryl groups discussed throughout this specification.

In a fourteenth embodiment of the compounds of structural formulae (I) and (Ia), R^2 and R^4 are each, independently of one another, an optionally substituted phenyl, aryl or heteroaryl, with the provisos that: (1) when L^1 is a direct bond and R^6 and optionally R^5 is hydrogen, then R^2 is other than 3,4,5-trimethoxyphenyl or 3,4,5-tri(C1-C6) alkoxyphenyl; (2) when L^1 and L^2 are each a direct bond, R^6 is hydrogen and R^5 is halo, then R^2 and R^4 are not each simultaneously 3,4,5-trimethoxyphenyl or 3,4,5-tri(C1-C6) alkoxyphenyl; (3) when R^4 is 3-methoxyphenyl or 3-(C1-C6) alkoxyphenyl and R^2 is a 3,4,5-trisubstituted phenyl, the substituents positioned at the 3 and 4 positions are not both simultaneously methoxy or (C1-C6) alkoxy; (4) when R^2 is a substituted phenyl and R^6 is hydrogen, then R^5 is other than cyano or –C(O)NHR, where R is hydrogen or (C1-C6) alkyl; and/or (5) when R^2 and R^4 are each independently a substituted or unsubstituted pyrrole or indole, then the pyrrole or indole is attached to the remainder of the molecule *via* a ring carbon atom. Alternatively, R^2 is subject to the provisos described in connection with the first or second embodiment.

In this fourteenth embodiment of the invention, the R^2 and R^4 substituents may be the same or different. Specific optionally substituted phenyl, aryl and/or heteroaryls include those illustrated above in connection with the twelfth and thirteenth embodiments.

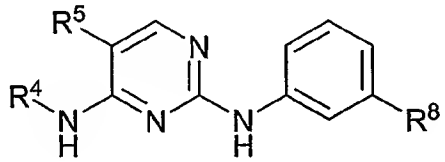
In a fifteenth embodiment of the compounds of structural formulae (I) and (Ia), including the above-described first through fourteenth embodiments thereof, R^6 is hydrogen and R^5 is an electronegative group. As will be recognized by skilled artisans, electronegative groups are atoms or groups of atoms that have a relatively great tendency to attract electrons to themselves. Specific examples of electronegative groups according to this fourteenth embodiment include, but are not limited to, -CN, -NC, $-NO_2$, halo, bromo, chloro, fluoro, (C1-C3) haloalkyl, (C1-C3) perhaloalkyl, (C1-C3) fluoroalkyl, (C1-C3) perfluoroalkyl, $-CF_3$, (C1-C3) haloalkoxy, (C1-C3) perhaloalkoxy, (C1-C3) fluoroalkoxy, (C1-C3) perfluoroalkoxy, $-OCF_3$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)CF_3$ and $-C(O)OCF_3$. In a specific embodiment, the electronegative group is a halogen-containing electronegative group, such as $–OCF_3$, $–CF_3$, bromo, chloro or fluoro. In another specific embodiment, R^5 is fluoro, subject to the proviso that the the compound is not any compound according to the third embodiment.

In a sixteenth embodiment, the compounds of structural formulae (I) and (Ia) are compounds according to structural formula (Ib):



and salts, hydrates, solvates and N-oxides thereof, wherein R^{11}, R^{12}, R^{13} and R^{14} are each, independently of one another, selected from the group consisting of hydrogen, hydroxy, (C1-C6) alkoxy and $-NR^cR^c$; and R^5, R^6 and R^c are as previously defined for structural formula (I), with the proviso that when R^{13}, R^5 and R^6 are each hydrogen, then R^{11} and R^{12} are not simultaneously methoxy, (C1-C6) alkoxy or (C1-C6) haloalkoxy

In a seventeenth embodiment, the compounds of structural formulae (I) and (Ia) are compounds according to structural formula (Ic):



and salts, hydrates, solvates and N-oxides thereof, wherein:

R^4 is selected from the group consisting of 5-10 membered heteroaryl and 3-hydroxyphenyl;

R^5 is F or $-CF_3$; and

R^8 is $-O(CH_2)_m-R^b$, where *m* and R^b are as previously defined for structural formula (I). In a specific embodiment, R^8 is $-O-CH_2-C(O)NH-CH_3$ and/or R^4 is a heteroaryl according to the thirteenth embodiment.

In an eighteenth embodiment, the compounds of structural formulae (I) and (Ia) include any compound selected from TABLE 1 that inhibits an Fc receptor signal transduction cascade, a Syk kinase activity, a Syk-kinase dependent receptor signal transduction cascade orcell degranulation as measured in an *in vitro* assay, optionally subject to the proviso that the compound is not a compound excluded by the above-described third embodiment and/or other embodiments. In a specific embodiment, such compounds have an IC_{50} of about 20 μM or less as measured in an *in vitro* degranulation assay, such as one of the degranulation assays described in the Examples section.

In a nineteenth embodiment, the compounds of structural formulae (I) and (Ia) include any compound selected from TABLE 1 that inhibits the FcγR1 or FcεR1 receptor

cascade with an IC_{50} of about 20 μM or less as measured in an *in vitro* assay, such as one of the *in vitro* assays provided in the Examples section, optionally subject to the proviso that the compound is not a compound excluded by the above-described third embodiment and/or other embodiments.

Also specifically described are combinations of the above first through nineteenth specific embodiments.

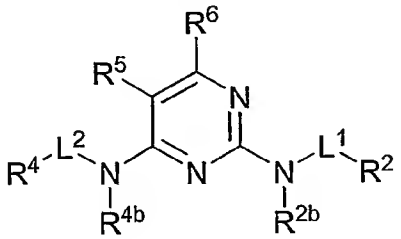
Those of skill in the art will appreciate that the 2,4-pyrimidinediamine compounds described herein may include functional groups that can be masked with progroups to ereate prodrugs. Such prodrugs are usually, but need not be, pharmacologically inactive until eonverted into their active drug form. Indeed, many of the active 2,4-pyrimidinediamine compounds described in TABLE 1, *infra*, include promoieties that are hydrolyzable or otherwise cleavable under conditions of use. For example, ester groups commonly undergo acid-catalyzed hydrolysis to yield the parent carboxylic acid when exposed to the acidic conditions of the stomach, or base-catalyzed hydrolysis when exposed to the basic conditions of the intestine or blood. Thus, when administered to a subject orally, 2,4-pyrimidinediamines that include ester moieties may be considered prodrugs of their corresponding carboxylic acid, regardless of whether the ester form is pharmacologically active. Referring to TABLE 1, numerous ester-containing 2,4-pyrimidinediamines of the invention are active in their ester, "prodrug" form.

In the prodrugs of the invention, any available functional moiety may be masked with a progroup to yield a prodrug. Functional groups within the 2,4-pyrimidinediamine compounds that may be masked with progroups for inclusion in a promoiety include, but are not limited to, amines (primary and secondary), hydroxyls, sulfanyls (thiols), carboxyls, etc. Myriad progroups suitable for masking such functional groups to yield promoieties that are cleavable under the desired conditions of use are known in the art. All of these progroups, alone or in combinations, may be included in the prodrugs of the invention.

In one illustrative embodiment, the prodrugs of the invention are compounds according to structural formula (I) in which R^c and R^d may be, in addition to their previously-defined alternatives, a progroup.

Replacing the hydrogens attached to N2 and N4 in the 2,4-pyrimidinediamines of structural formula (I) with substituents adversely effects the activity of the compounds. However, as will be appreciated by skilled artisans, these nitrogens may be included in promoieties that, under conditions of use, cleave to yield 2,4-pyrimidinediamines according

to structural formula (I). Thus, in another embodiment, the prodrugs of the invention are compounds according to structural formula (II):



including salts, hydrates, solvates and N-oxides thereof, wherein:

R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for structural formula (I); and

R^{2b} and R^{4b} are each, independently of one another, a progroup. Specific examples of progroups according to this embodiment of the invention include, but are not limited to, (C1-C6) alkyl, $-C(O)CH_3$, $-C(O)NHR^{36}$ and $-S(O)_2R^{36}$, where R^{36} is (C1-C6) alkyl, (C5-C15) aryl and (C3-C8) cycloalkyl.

In the prodrugs of structural formula (II), the various substituents may be as described for the various first through twentieth embodiments previously described for the compounds of structural formulae (I) and (Ia), or combinations of such embodiments.

Those of skill in the art will appreciate that many of the compounds and prodrugs of the invention, as well as the various compound species specifically described and/or illustrated herein, may exhibit the phenomena of tautomerism, conformational isomerism, geometric isomerism and/or optical isomerism. For example, the compounds and prodrugs of the invention may include one or more chiral centers and/or double bonds and as a consequence may exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers and diasteromers and mixtures thereof, such as racemic mixtures. As another example, the compounds and prodrugs of the invention may exist in several tautomeric forms, including the enol form, the keto form and mixtures thereof. As the various compound names, formulae and compound drawings within the specification and claims can represent only one of the possible tautomeric, conformational isomeric, optical isomeric or geometric isomeric forms, it should be understood that the invention encompasses any tautomeric, conformational isomeric, optical isomeric and/or geometric isomeric forms of the compounds or prodrugs having one or more of the utilities described herein, as well as mixtures of these various different isomeric forms. In cases of limited rotation around the 2,4-pryimidinediamine core structure, atrop isomers are also possible and are also specifically included in the compounds of the invention.

Moreover, skilled artisans will appreciate that when lists of alternative substituents include members which, owing to valency requirements or other reasons, cannot be used to substitute a particular group, the list is intended to be read in context to include those members of the list that are suitable for substituting the particular group. For example, skilled artisans will appreciate that while all of the listed alternatives for R^b can be used to substitute an alkyl group, certain of thc alternatives, such as =O, cannot be used to substitute a phenyl group. It is to bc understood that only possible combinations of substituent-group pairs are intended.

The eompounds and/or prodrugs of the invention may be identified by either their chemical structure or their chemical name. When the chemical structure and the chemical name conflict, the chemical structure is determinative of the identity of the specific compound.

Depending upon the nature of the various substituents, the 2,4-pyrimidinediamine compounds and prodrugs of the invention may be in the form of salts. Sueh salts include salts suitable for pharmaceutical uses ("pharmaceutically-acceptable salts"), salts suitable for veterinary uses, etc. Such salts may be derived from acids or bases, as is well-known in the art.

In one embodiment, the salt is a pharmaceutically acceptable salt. Generally, pharmaceutically acceptable salts are those salts that retain substantially one or more of the desired pharmacological activities of the parent compound and which are suitable for administration to humans. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids or organic acids. Inorganic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, hydrohalide acids (*e.g.*, hydrochloric acid, hydrobromic acid, hydriodic, etc.), sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids suitable for forming pharmaceutically acceptable acid addition salts include, by way of example and not limitation, acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, oxalic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, palmitic acid, benzoic aeid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, alkylsulfonic acids (*e.g.*, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, etc.), arylsulfonie acids (*e.g.*, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, etc.), 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid,

glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

Pharmaceutically acceptable salts also include salts formed when an acidic proton present in the parent compound is either replaced by a metal ion (*e.g.*, an alkali metal ion, an alkaline earth metal ion or an aluminum ion) or coordinates with an organic base (*e.g.*, ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, piperidine, dimethylamine, diethylamine, etc.).

The 2,4-pyrimidinediamine compounds and of the invention, as well as the salts thereof, may also be in the form of hydrates, solvates and N-oxides, as are well-known in the art.

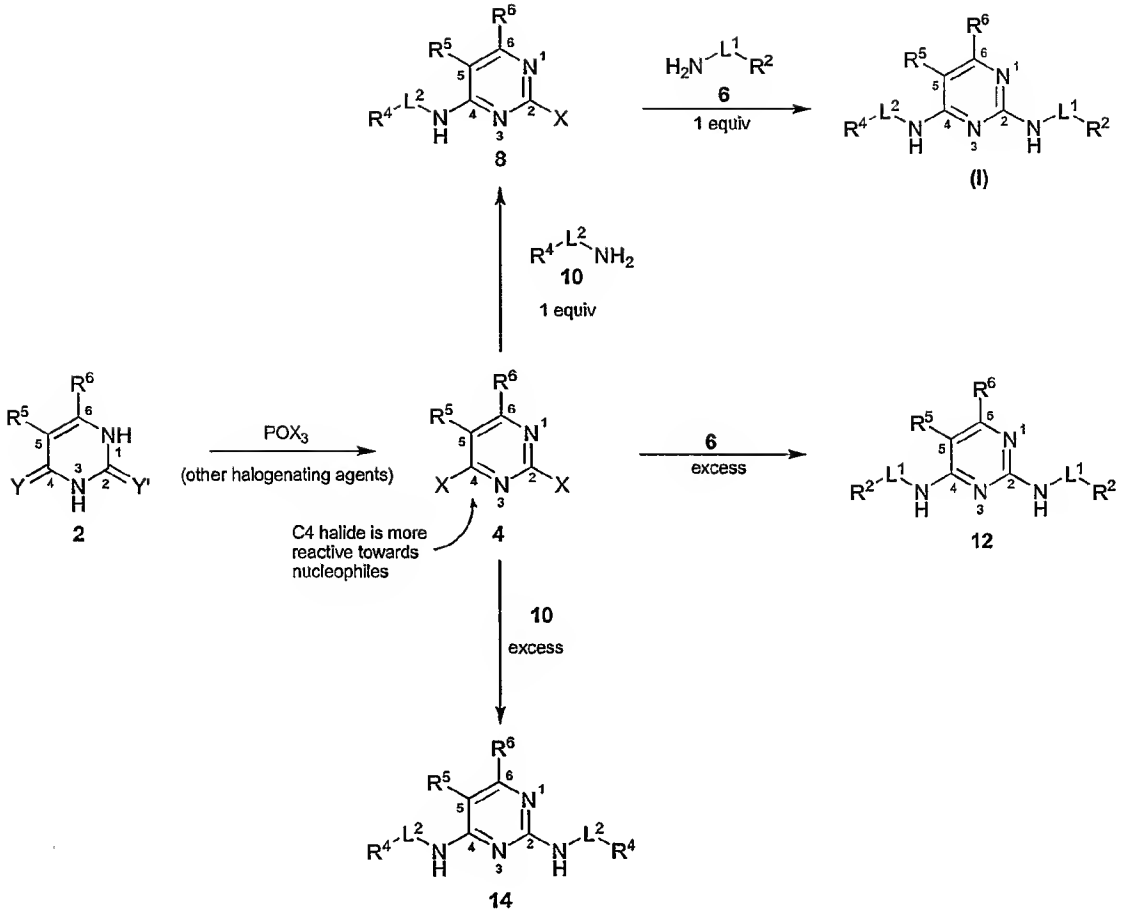
6.3 Methods of Synthesis

The compounds and prodrugs of the invention may be synthesized *via* a variety of different synthetic routes using commercially available starting materials and/or starting materials prepared by conventional synthetic methods. Suitable exemplary methods that may be routinely adapted to synthesize the 2,4-pyrimidinediamine compounds and prodrugs of the invention are found in U.S. Patent No. 5,958,935, the disclosure of which is incorporated herein by reference. Specific examples describing the synthesis of numerous compounds and prodrugs of the invention, as well as intermediates therefor, are provided in the Examples section. All of the compounds of structural formulae (I), (Ia) and (II) may be prepared by routine adaptation of these methods.

A variety of exemplary synthetic routes that can be used to synthesize the 2,4-pyrimidinediamine compounds of the invention are described in Schemes (I)-(XI), below. In Schemes (I)-(XI), like-numbered compounds have similar structures. These methods may be routinely adapted to synthesize the prodrugs according to structural formula (II).

In one exemplary embodiment, the compounds can be synthesized from substituted or unsubstituted uracils or thiouracils as illustrated in Scheme (I), below:

Scheme (I)



In Scheme (I), R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for structural formula (I), X is a halogen (*e.g.*, F, Cl, Br or I) and Y and Y' are each, independently of one another, selected from the group consisting of O and S. Referring to Scheme (I), uracil or thiouracil **2** is dihalogenated at the 2- and 4-positions using standard halogenating agent POX_3 (or other standard halogenating agent) under standard conditions to yield 2,4-bishalo pyrimidine **4**. Depending upon the R^5 substituent, in pyrimidine **4**, the halide at the C4 position is more reactive towards nucleophiles than the halide at the C2 position. This differential reactivity can be exploited to synthesize 2,4-pyrimidinediamines according structural formula (I) by first reacting 2,4-bishalopyrimidine **4** with one equivalent of amine **10**, yielding 4N-substituted-2-halo-4-pyrimidineamine **8**, followed by amine **6** to yield a 2,4-pyrimidinediamine according structural formula **(I)**. 2N,4N-bis(substituted)-2,4-pyrimidinediamines **12** and **14** can be obtained by reacting 2,4-bishalopyrimidine **4** with excess **6** or **10**, respectively.

In most situations, the C4 halide is more reactive towards nucleophiles, as illustrated in the Scheme. However, as will be recognized by skilled artisans, the identity of the R^5 substituent may alter this reactivity. For example, when R^5 is trifluoromethyl, a 50:50 mixture of 4N-substituted-4-pyrimidineamine **8** and the corresponding 2N-substituted-2-pyrimidineamine is obtained. Regardless of the identity of the R^5 substituent, the regioselectivity of the reaction can be controlled by adjusting the solvent and other synthetic conditions (such as temperature), as is well-known in the art.

The reactions depicted in Scheme (I) may proceed more quickly when the reaction mixtures are heated *via* microwave. When heating in this fashion, the following conditions may be used: heat to 175°C in ethanol for 5-20 min. in a Smith Reactor (Personal Chemistry) in a sealed tube (at 20 bar pressure).

The uracil or thiouracil **2** starting materials may be purchased from commercial sources or prepared using standard techniques of organic chemistry. Commercially available uracils and thiouracils that can be used as starting materials in Scheme (I) include, by way of example and not limitation, uracil (Aldrich #13,078-8; CAS Registry 66-22-8); 2-thio-uracil (Aldrich #11,558-4; CAS Registry 141-90-2); 2,4-dithiouracil (Aldrich #15,846-1; CAS Registry 2001-93-6); 5-acetouracil (Chem. Sources Int'l 2000; CAS Registry 6214-65-9); 5-azidouracil; 5-aminouracil (Aldrich #85,528-6; CAS Registry 932-52-5); 5-bromouracil (Aldrich #85,247-3; CAS Registry 51-20-7); 5-(trans-2-bromovinyl)-uracil (Aldrich #45,744-2; CAS Registry 69304-49-0); 5-(trans-2-chlorovinyl)-uracil (CAS Registry 81751-48-2); 5-(trans-2-carboxyvinyl)-uracil; uracil-5-carboxylic acid (2,4-dihydroxypyrimidine-5-carboxylic acid hydrate; Aldrich #27,770-3; CAS Registry 23945-44-0); 5-chlorouracil (Aldrich #22,458-8; CAS Registry 1820-81-1); 5-cyanouracil (Chem. Sources Int'l 2000; CAS Registry 4425-56-3); 5-ethyluracil (Aldrich #23,044-8; CAS Registry 4212-49-1); 5-ethenyluracil (CAS Registry 37107-81-6); 5-fluorouracil (Aldrich #85,847-1; CAS Registry 51-21-8); 5-iodouracil (Aldrich #85,785-8; CAS Registry 696-07-1); 5-methyluracil (thymine; Aldrich #13,199-7; CAS Registry 65-71-4); 5-nitrouracil (Aldrich #85,276-7; CAS Registry 611-08-5); uracil-5-sulfamic acid (Chem. Sources Int'l 2000; CAS Registry 5435-16-5); 5-(trifluoromethyl)-uracil (Aldrich #22,327-1; CAS Registry 54-20-6); 5-(2,2,2-trifluoroethyl)-uracil (CAS Registry 155143-31-6); 5-(pentafluoroethyl)-uracil (CAS Registry 60007-38-3); 6-aminouracil (Aldrich #A5060-6; CAS Registry 873-83-6) uracil-6-carboxylic acid (orotic acid; Aldrich #0-840-2; CAS Registry 50887-69-9); 6-methyluracil (Aldrich #D11,520-7; CAS Registry 626-48-2); uracil-5-amino-6-carboxylic acid (5-aminoorotic acid; Aldrich #19,121-3; CAS Registry

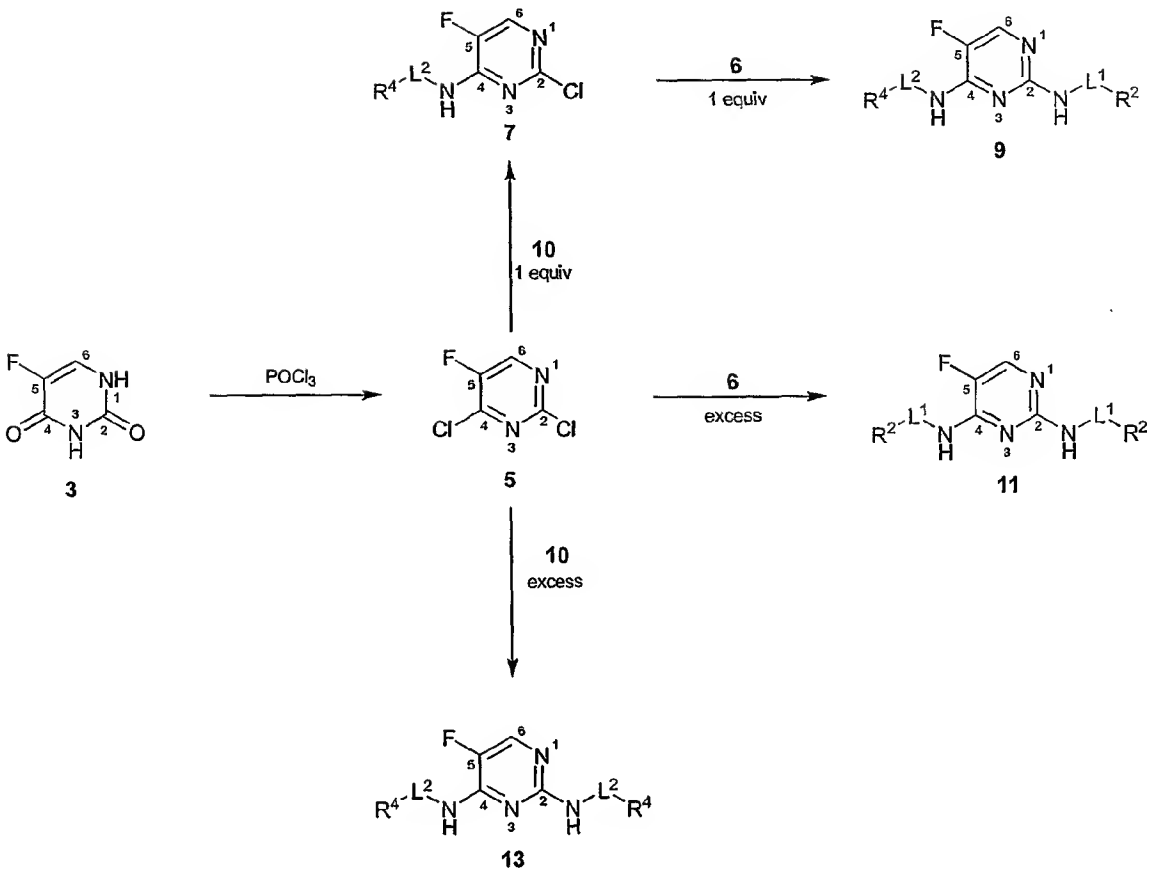
#7164-43-4); 6-amino-5-nitrosouracil (6-amino-2,4-dihydroxy-5-nitrosopyrimidine; Aldrich #27,689-8; CAS Registry 5442-24-0); uracil-5-fluoro-6-carboxylic acid (5-fluoroorotic acid; Aldrich #42,513-3; CAS Registry 00000-00-0); and uracil-5-nitro-6-carboxylic acid (5-nitroorotic acid; Aldrich #18,528-0; CAS Registry 600779-49-9). Additional 5-, 6- and 5,6-substituted uracils and/or thiouracils are available from General Intermediates of Canada, Inc., Edmonton, CA (www.generalintermediates.com) and/or Interchim, Cedex, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

Amines **6** and **10** may be purchased from commercial sources or, alternatively, may be synthesized utilizing standard techniques. For example, suitable amines may be synthesized from nitro precursors using standard chemistry. Specific exemplary reactions are provided in the Examples section. See also Vogel, 1989, *Practical Organic Chemistry*, Addison Wesley Longman, Ltd. and John Wiley & Sons, Inc.

Skilled artisans will recognize that in some instances, amines **6** and **10** and/or substituents R^5 and/or R^6 on uracil or thiouracil **2** may include functional groups that require protection during synthesis. The exact identity of any protecting group(s) used will depend upon the identity of the functional group being protected, and will be apparent to these of skill in the art. Guidance for selecting appropriate protecting groups, as well as synthetic strategies for their attachment and removal, may be found, for example, in Greene & Wuts, *Protective Groups in Organic Synthesis*, 3d Edition, John Wiley & Sons, Inc., New York (1999) and the references cited therein (hereinafter "Greene & Wuts").

A specific embodiment of Scheme (I) utilizing 5-fluorouracil (Aldrich #32,937-1) as a starting material is illustrated in Scheme (Ia), below:

Scheme (Ia)

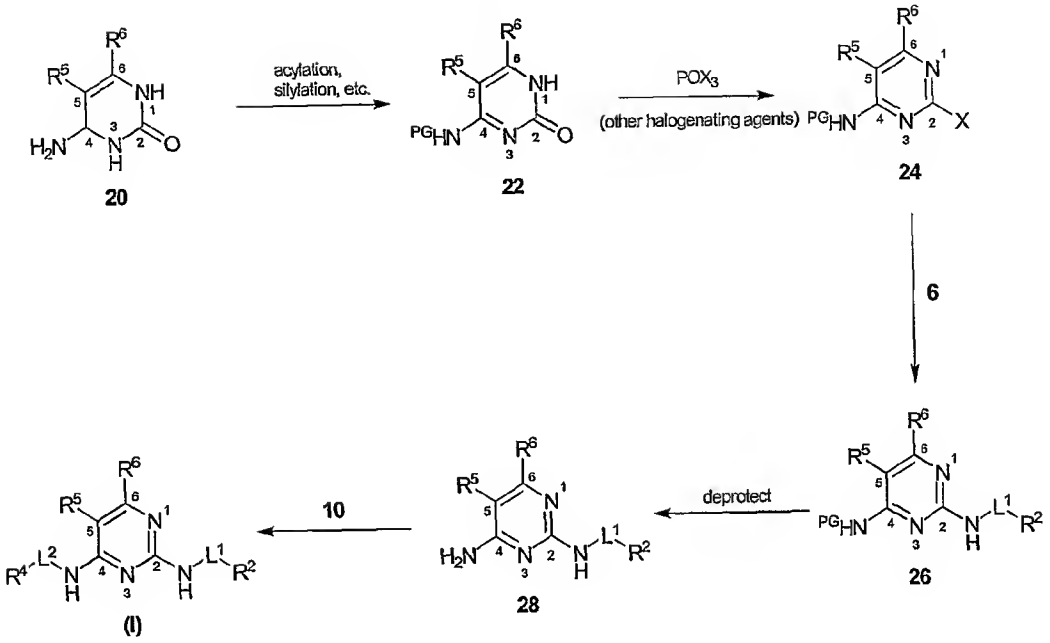


In Scheme (Ia), R^2, R^4, L^1 and L^2 are as previously defined for Scheme (I).

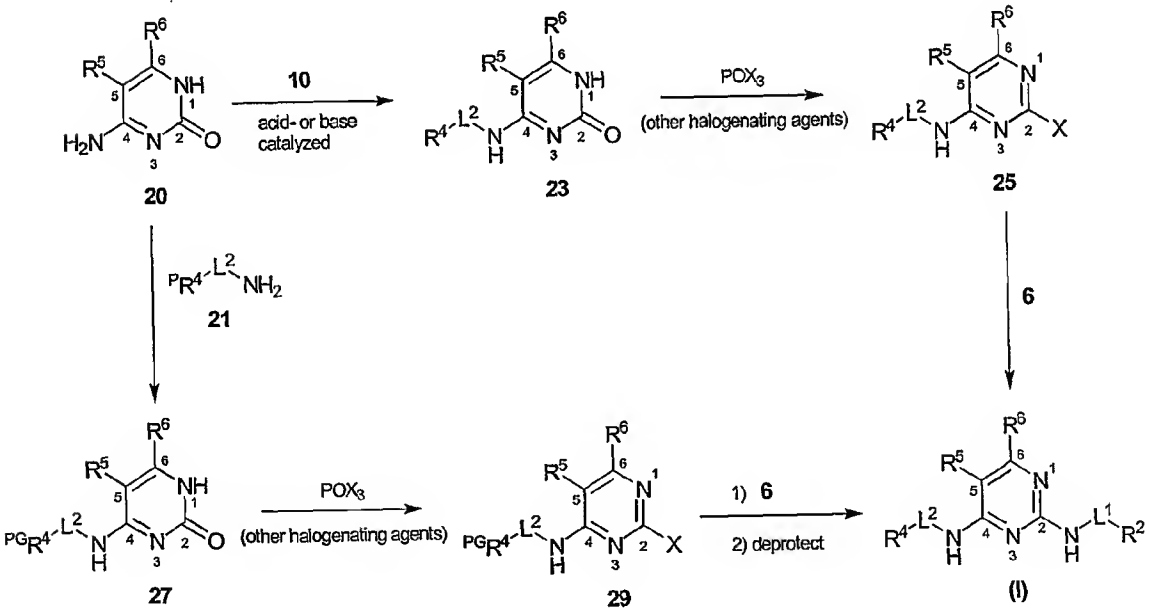
According to Scheme (Ia), 5-fluorouracil **3** is halogenated with $POCl_3$ to yield 2,4-dichloro-5-fluoropyrimidine **5**, which is then reacted with excess amine **6** or **10** to yield N2,N4-bis substituted 5-fluoro-2,4-pyrimidinediamine **11** or **13**, respectively. Alternatively, asymmetric 2N,4N-disubstituted-5-fluoro-2,4-pyrimidinediamine **9** may be obtained by reacting 2,4-dichloro-5-fluoropyrimidine **5** with one equivalent of amine **10** (to yield 2-chloro-N4-substituted-5-fluoro-4-pyrimidineamine **7**) followed by one or more equivalents of amine **6**.

In another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention may be synthesized from substituted or unsubstituted cytosines as illustrated in Schemes (IIa) and (IIb), below:

Scheme (IIa)



Scheme (IIb)



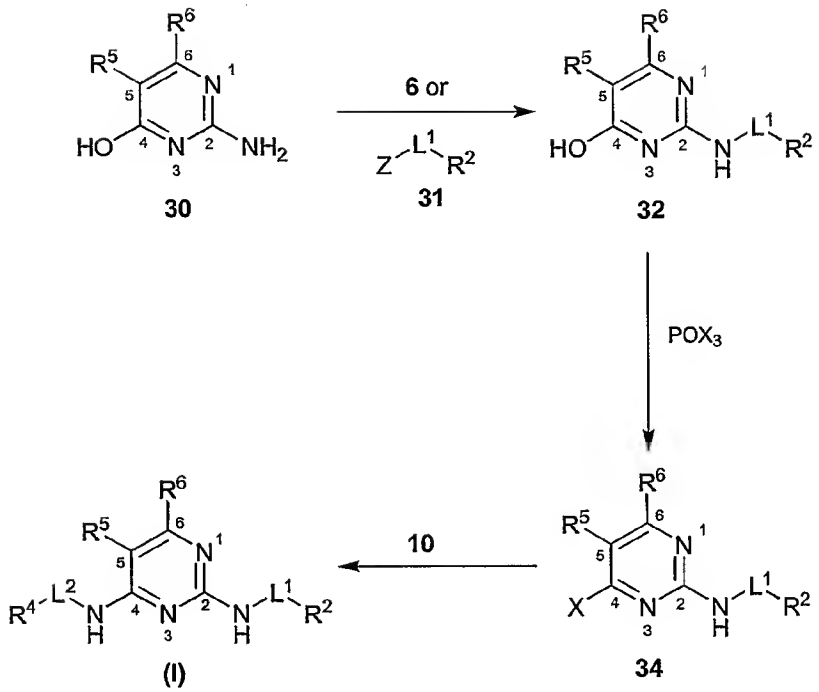
In Schemes (IIa) and (IIb), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined for Scheme (I) and PG represents a protecting group. Referring to Scheme (IIa), the C4 exocyclic amine of cytosine **20** is first protected with a suitable protecting group PG to yield N4-protected cytosine **22**. For specific guidance regarding protecting groups useful in this context, *see* Vorbrüggen and Ruh-Pohlenz, 2001, *Handbook of Nucleoside Synthesis*, John Wiley & Sons, NY, pp. 1-631 ("Vorbrüggen"). Protected cytosine **22** is halogenated at the C2 position using a standard halogenation reagent under standard conditions to yield 2-chloro-4N-protected-4-pyrimidineamine **24**. Reaction with amine **6** followed by deprotection of the C4 exocyclic amine and reaction with amine **10** yields a 2,4-pyrimidinediamine according to structural formula **(I)**.

Alternatively, referring to Scheme (IIb), cytosine **20** may be reacted with amine **10** or protected amine **21** to yield N4-substituted cytosine **23** or **27**, respectively. These substituted cytosines may then be halogenated as previously described, deprotected (in the case of N4-substituted cytosine **27**) and reacted with amine **6** to yield a 2,4-pyrimidinediamine according to structural formula **(I)**.

Commercially-available cytosines that may be used as starting materials in Schemes (IIa) and (IIb) include, but are not limited to, cytosine (Aldrich #14,201-8; CAS Registry 71-30-7); N^4-acetylcytosine (Aldrich #37,791-0; CAS Registry 14631-20-0); 5-fluorocytosine (Aldrich #27,159-4; CAS Registry 2022-85-7); and 5-(trifluoromethyl)-cytosine. Other suitable cytosines useful as starting materials in Schemes (IIa) are available from General Intermediates of Canada, Inc., Edmonton, CA (www.generalintermediates.com) and/or Interchim, Cedex, France (www.interehim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

In still another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention may be synthesized from substituted or unsubstituted 2-amino-4-pyrimidinols as illustrated in Scheme (III), below:

Scheme (III)

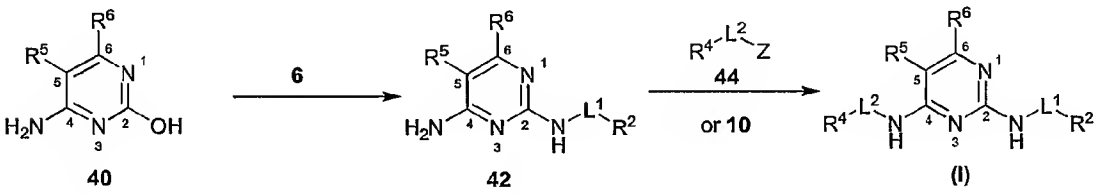


In Scheme (III), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined for Scheme (I) and Z is a leaving group as discussed in more detail in connection with Scheme IV, *infra*. Referring to Scheme (III), 2-amino-4-pyrimidinol **30** is reacted with amine **6** (or optionally protected amine **21**) to yield N2-substituted-4-pyrimidinol **32**, which is then halogenated as previously described to yield N2-substituted-4-halo-2-pyrimidineamine **34**. Optional deprotection (for example if protected amine **21** was used in the first step) followed by reaction with amine **10** affords a 2,4-pyrimidinediamine according to structural formula **(I)**. Alternatively, pyrimidinol **30** can be reacted with acylating agent **31**.

Suitable commercially-available 2-amino-4-pyrimidinols **30** that can be used as starting materials in Scheme (III) include, but are not limited to, 2-amino-6-chloro-4-pyrimidinol hydrate (Aldrich #A4702-8; CAS Registry 00000-00-0) and 2-amino-6-hydroxy-4-pyrimidinol (Aldrich #A5040-1; CAS Registry 56-09-7). Other 2-amino-4-pyrimidinols **30** useful as starting materials in Scheme (III) are available from General Intermediates of Canada, Inc., Edmonton, CA (www.generalintermediates.com) and/or Interchim, Cedex, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

Alternatively, the 2,4-pyrimidinediamine compounds of the invention may be prepared from substituted or unsubstituted 4-amino-2-pyrimidinols as illustrated in Scheme (IV), below:

Scheme (IV)

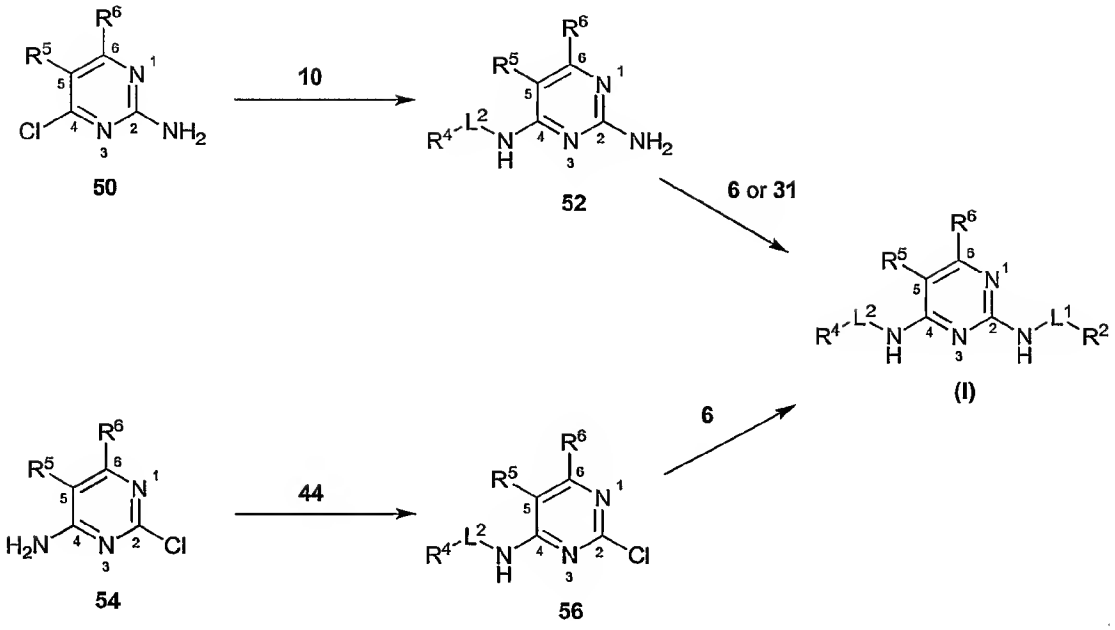


In Scheme (IV), R^2, R^4, R^5, R^6, L^1 and L^2 are as previously defined for Scheme (I) and Z represents a leaving group. Referring to Scheme (IV), the C2-hydroxyl of 4-amino-2-pyrimidinol **40** is more reactive towards nucleophiles than the C4-amino such that reaction with amine **6** yields N2-substituted-2,4-pyrimidinediamine **42**. Subsequent reaction with compound **44**, which includes a good leaving group Z, or amine **10** yields a 2,4-pyrimidinediamine according to structural formula **(I)**. Compound **44** may include virtually any leaving group that can be displaced by the C4-amino of N2-substituted-2,4-pyrimidinediamine **42**. Suitable leaving groups Z include, but are not limited to, halogens, methanesulfonyloxy (mesyloxy; "OMs"), trifluoromethanesulfonyloxy ("OTf") and *p*-toluenesulfonyloxy (tosyloxy; "OTs"), benzene sulfonyloxy ("besylate") and metanitro benzene sulfonyloxy ("nosylate"). Other suitable leaving groups will be apparent to those of skill in the art.

Substituted 4-amino-2-pyrimidinol starting materials may be obtained commercially or synthesized using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

In still another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention can be prepared from 2-chloro-4-aminopyrimidines or 2-amino-4-chloropyrimidines as illustrated in Scheme (V), below:

Scheme (V)

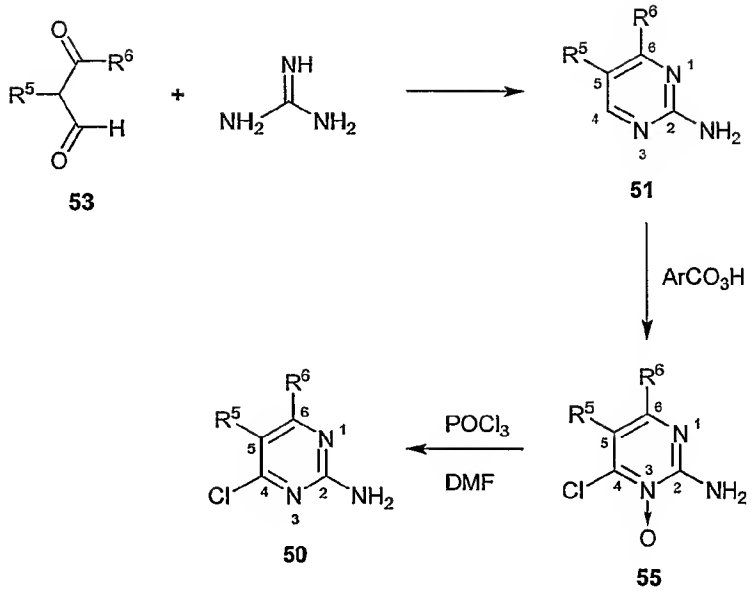


In Scheme (V), R^2, R^4, R^5, R^6, L^1, L^2 and X are as defined for Scheme (I) and Z is as defined for Scheme (IV). Referring to Scheme (V), 2-amino-4-chloropyrimidine **50** is reacted with amino **10** to yield 4N-substituted-2-pyrimidineamine **52** which, following reaction with compound **31** or amine **6**, yields a 2,4-pyrimidinediamine according to structural formula **(I)**. Alternatively, 2-chloro-4-amino-pyrimidine **54** may be reacted with compound **44** followed by amine **6** to yield a compound according to structural formula **(I)**.

A variety of pyrimidines **50** and **54** suitable for use as starting materials in Scheme (V) are commercially available, including by way of example and not limitation, 2-amino-4,6-dichloropyrimidine (Aldrich #A4860-1; CAS Registry 56-05-3); 2-amino-4-chloro-6-methoxy-pyrimidine (Aldrich #51,864-6; CAS Registry 5734-64-5); 2-amino-4-chloro-6-methylpyrimidine (Aldrich #12,288-2; CAS Registry 5600-21-5); and 2-amino-4-chloro-6-methylthiopyrimidine (Aldrich #A4600-5; CAS Registry 1005-38-5). Additional pyrimidine starting materials are available from General Intermediates of Canada, Inc., Edmonton, CA (www.generalintermediates.eom) and/or Interchim, Cedex, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

Alternatively, 4-chloro-2-pyrimidineamines **50** may be prepared as illustrated in Scheme (Va):

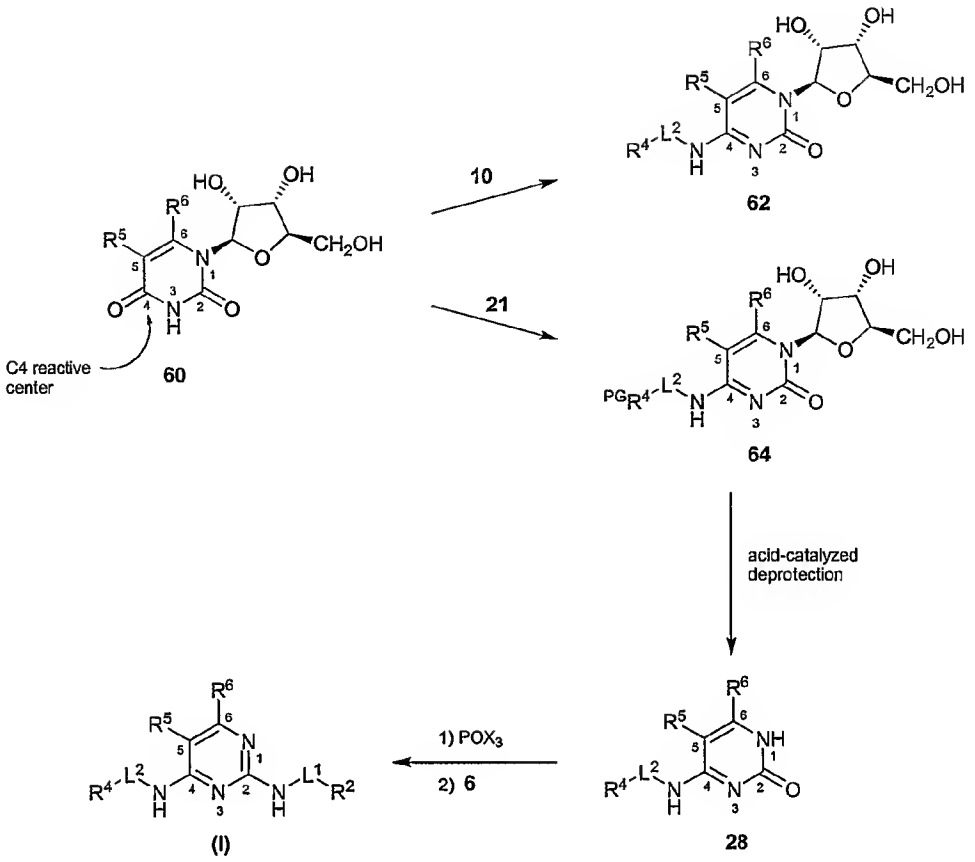
Scheme (Va)



In Scheme (Va), R^5 and R^6 are as previously defined for structural formula (I). In Scheme (Va), dicarbonyl **53** is reacted with guanidine to yield 2-pyrimidineamine **51**. Reaction with peracids like m-chloroperbenzoic acid, trifluoroperacetic acid or urea hydrogen peroxide complex yields N-oxide **55**, which is then halogenated to give 4-chloro-2-pyrimidineamine **50**. The corresponding 4-halo-2-pyrimidineamines may be obtained by using suitable halogenation reagents.

In yet another exemplary embodiment, the 2,4-pyrimidinediamine compounds of the invention can be prepared from substituted or unsubstituted uridines as illustrated in Scheme (VI), below:

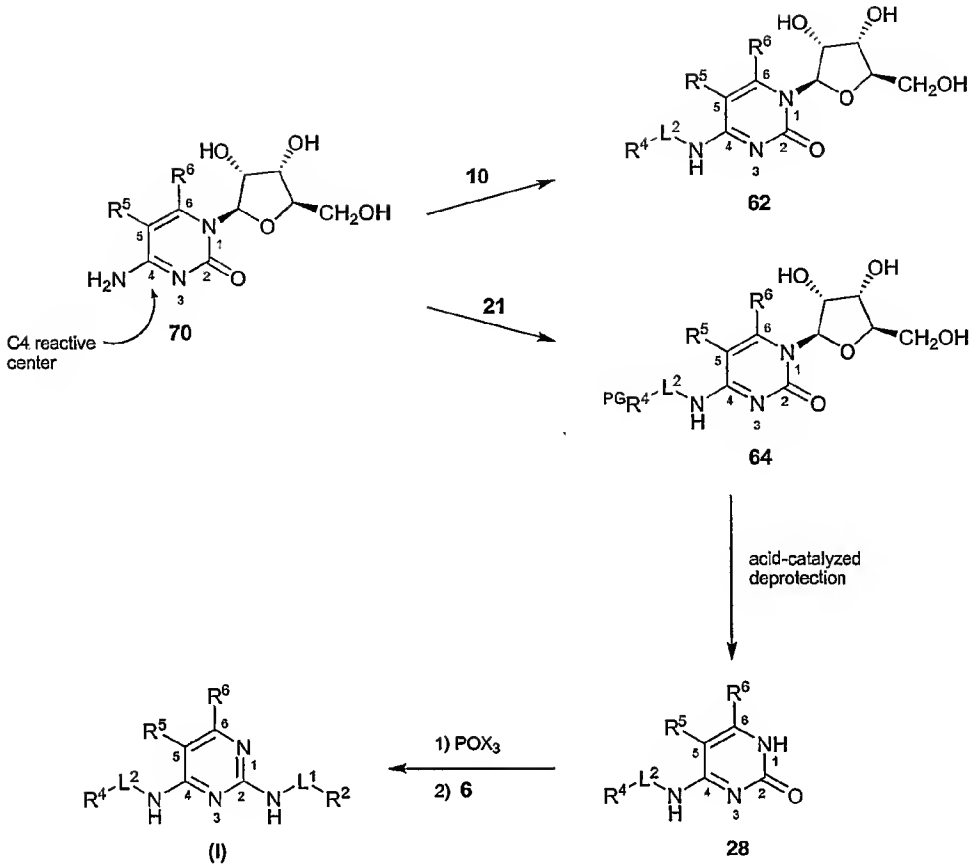
Scheme (VI)



In Scheme (VI), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined for Scheme (I) and the superscript PG represents a protecting group, as discussed in connection with Scheme (IIb). According to Scheme (VI), uridine **60** has a C4 reactive center such that reaction with amine **10** or protected amine **21** yields N4-substituted cytidine **62** or **64**, respectively. Acid-catalyzed deprotection of N4-substituted **62** or **64** (when "PG" represents an acid-labile protecting group) yields N4-substituted cytosine **28**, which may be subsequently halogenated at the C2-position and reacted with amine **6** to yield a 2,4-pyrimidinediamine according to structural formula **(I)**.

Cytidines may also be used as starting materials in an analogous manner, as illustrated in Scheme (VII), below:

Scheme (VII)



In Scheme (VII), R^2, R^4, R^5, R^6, L^1, L^2 and X are as previously defined in Scheme (I) and the superscript PG represents a protecting group as discussed above. Referring to Scheme (VII), like uridine **60**, cytidine **70** has a C4 reactive center such that reaction with amine **10** or protected amine **21** yields N4-substituted cytidine **62** or **64**, respectively. These cytidines **62** and **64** are then treated as previously described for Scheme (VI) to yield a 2,4-pyrimidinediamine according to structural formula **(I)**.

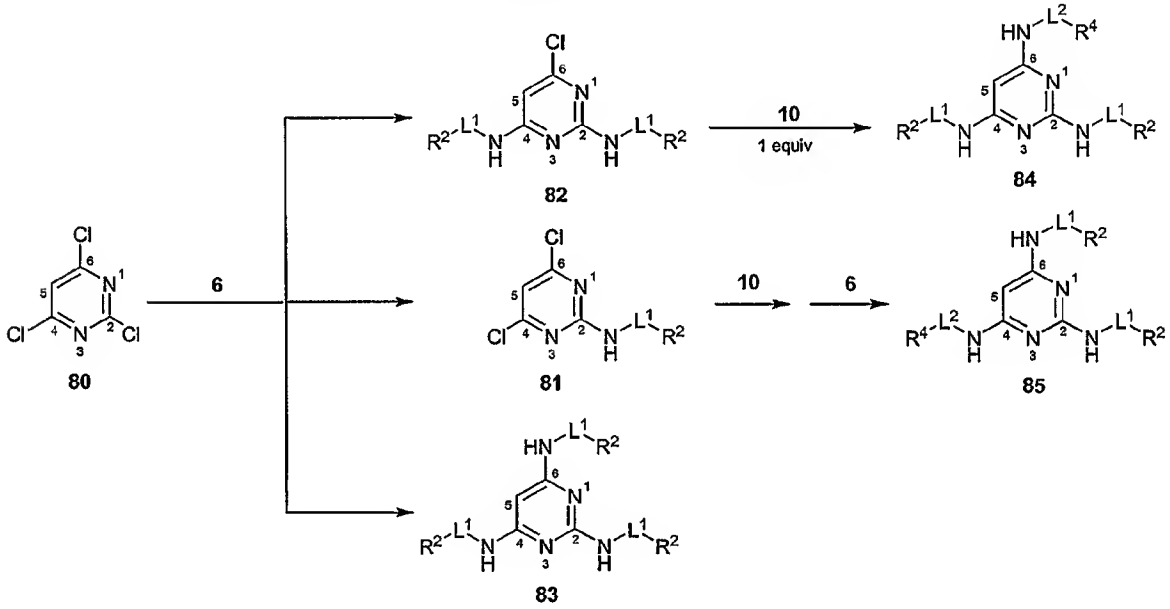
Although Schemes (VI) and (VII) are exemplified with ribosylnucleosides, skilled artisans will appreciate that the corresponding 2'-deoxyribo and 2',3'-dideoxyribo nucleosides, as well as nucleosides including sugars or sugar analogs other than ribose, would also work.

Numerous uridines and cytidines useful as starting materials in Schemes (VI) and (VII) are known in the art, and include, by way of example and not limitation, 5-trifluoromethyl-2'-deoxycytidine (Chem. Sources #ABCR F07669; CAS Registry 66,384-66-5); 5-bromouridine (Chem. Sources Int'l 2000; CAS Registry 957-75-5); 5-iodo-2'-deoxyuridine (Aldrich #1-775-6; CAS Registry 54-42-2); 5-fluorouridine (Aldrich #32,937-1; CAS Registry 316-46-1); 5-iodouridine (Aldrich #85,259-7; CAS

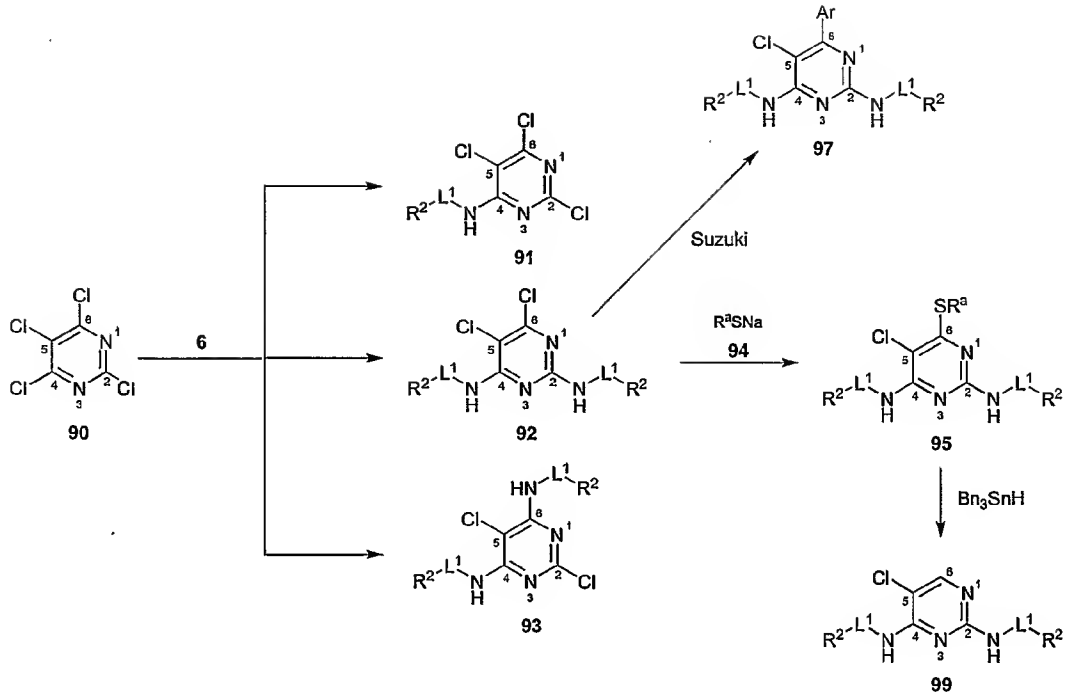
Registry 1024-99-3); 5-(trifluoromethyl)uridine (Chem. Sources Int'l 2000; CAS Registry 70-00-8); 5-trifluoromethyl-2'-deoxyuridine (Chem. Sources Int'l 2000; CAS Registry 70-00-8). Additional uridines and cytidines that can be used as starting materials in Schemes (VI) and (VII) are available from General Intermediates of Canada, Inc., Edmonton, CA (www.generalintermediates.com) and/or Interchim, Cedex, France (www.interchim.com), or may be prepared using standard techniques. Myriad textbook references teaching suitable synthetic methods are provided *infra*.

The 2,4-pyrimidinediamine compounds of the invention can also be synthesized from substituted pyrimidines, such as chloro-substituted pyrimidines, as illustrated in Schemes (VIII) and (IX), below:

Scheme (VIII)



Scheme (IX)



In Schemes (VIII) and (IX), R^2, R^4, L^1, L^2 and R^a are as previously defined for structural formula (I) and "Ar" represents an aryl group. Referring to Scheme (VIII), reaction of 2,4,6-trichloropyrimidine **80** (Aldrich #T5,620-0; CAS#3764-01-0) with amine **6** yields a mixture of three compounds: substituted pyrimidine mono-, di- and triamines **81, 82** and **83**, which can be separated and isolated using HPLC or other conventional techniques. Mono- and diamines **81** and **82** may be further reacted with amines **6** and/or **10** to yield N2,N4,N6-trisubstituted-2,4,6-pyrimidinetriamines **84** and **85**, respectively.

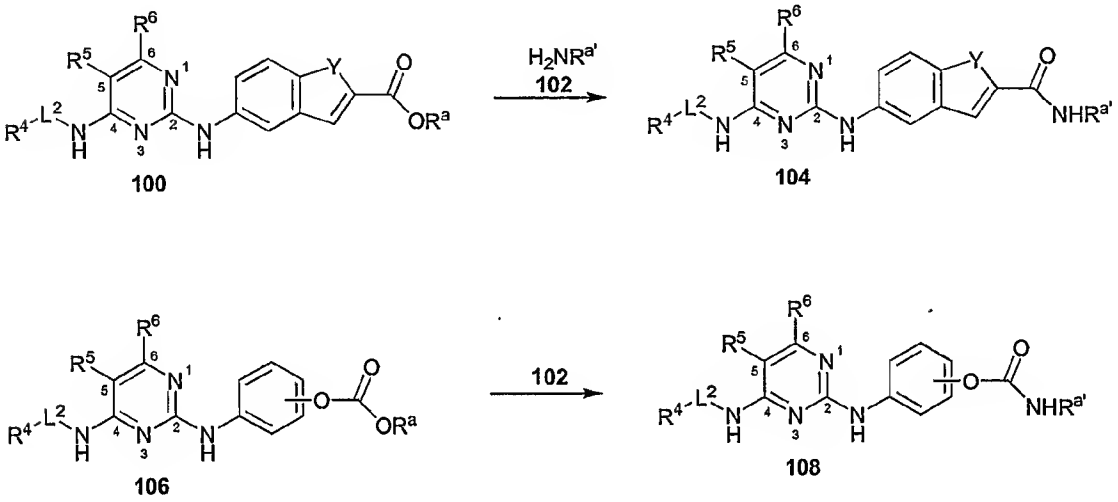
N2,N4-bis-substituted-2,4-pyrimidinediamines can be prepared in a manner analogous to Scheme (VIII) by employing 2,4-dichloro-5-methylpyrimidine or 2,4-dichloro-pyrimidine as starting materials. In this instance, the mono-substituted pyrimidineamine corresponding to compound **81** is not obtained. Instead, the reaction proceeds to yield the N2,N4-bis-substituted-2,4-pyrimidinediamine directly.

Referring to Scheme (IX), 2,4,5,6-tetrachloropyrimidine **90** (Aldrich #24,671-9; CAS#1780-40-1) is reacted with excess amine **6** to yield a mixture of three compounds: **91, 92,** and **93**, which can be separated and isolated using HPLC or other conventional techniques. As illustrated, N2,N4-bis-substituted-5,6,-dichloro-2,4-pyrimidinediamine **92** may be further reacted at the C6 halide with, for example a nucleophilic agent **94** to yield compound **95**. Alternatively, compound **92** can be converted into N2,N4-bis-subsituted-5-

chloro-6-aryl-2,4-pyrimidinediamine **97** *via* a Suzuki reaction. 2,4-Pyrimidinediamine **95** may be converted to 2,4-pyrimidinediamine **99** by reaction with Bn_3SnH.

As will be recognized by skilled artisans, 2,4-pyrimidinediamines according to the invention, synthesized *via* the exemplary methods described above or by other well-known means, may also be utilized as starting materials and/or intermediates to synthesize additional 2,4-pyrimidinediamine compounds of the invention. A specific example is illustrated in Scheme (X), below:

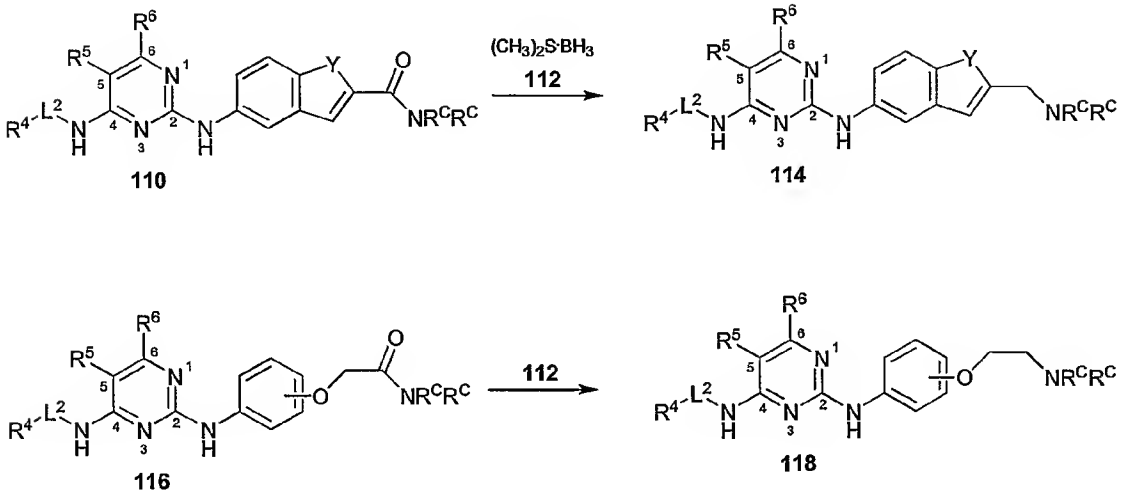
Scheme (X)



In Scheme (X), R^4, R^5, R^6, L^2 and R^a are as previously defined for structural formula (I). Each $R^{a'}$ is independently an R^a, and may be the same or different from the illustrated R^a. Referring to Scheme (X), carboxylic acid or ester **100** may be converted to amide **104** by reaction with amine **102**. In amine **102**, $R^{a'}$ may be the same or different than R^a of acid or ester **100**. Similarly, carbonate ester **106** may be converted to carbamate **108**.

A second specific example is illustrated in Scheme (XI), below:

Scheme (XI)



In Scheme (XI), R^4, R^5, R^6, L^2 and R^c are as previously defined for structural formula (I). Referring to Scheme (XI), amide **110** or **116** may be converted to amine **114** or **118**, respectively, by borane reduction with borane methylsulfide complex **112**. Other suitable reactions for synthesizing 2,4-pyrimidinediamine compounds from 2,4-pyrimidinediamine starting materials will be apparent to those of skill in the art.

Although many of the synthetic schemes discussed above do not illustrate the use of protecting groups, skilled artisans will recognize that in some instances substituents R^2, R^4, R^5, R^6, L^1 and/or L^2 may include functional groups requiring protection. The exact identity of the protecting group used will depend upon, among other things, the identity of the functional group being protected and the reaction conditions used in the particular synthetic scheme, and will be apparent to those of skill in the art. Guidance for selecting protecting groups and chemistries for their attachment and removal suitable for a particular application can be found, for example, in Greene & Wuts, *supra*.

Prodrugs according to structural formula (II) may be prepared by routine modification of the above-described methods. Alternatively, such prodrugs may be prepared by reacting a suitably protected 2,4-pyrimidinediamine of structural formula (I) with a suitable progroup. Conditions for carrying out such reactions and for deprotecting the product to yield a prodrug of formula (II) are well-known.

Myriad references teaching methods useful for synthesizing pyrimidines generally, as well as starting materials described in Schemes (I)-(IX), are known in the art. For

specific guidance, the reader is referred to Brown, D. J., "The Pyrimidines", in *The Chemistry of Heterocyclic Compounds, Volume 16* (Weissberger, A., Ed.), 1962, Interscience Publishers, (A Division of John Wiley & Sons), New York ("Brown I"); Brown, D. J., "The Pyrimidines", in *The Chemistry of Heterocyclic Compounds, Volume 16, Supplement I* (Weissberger, A. and Taylor, E. C., Ed.), 1970, Wiley-Interscience, (A Division of John Wiley & Sons), New York (Brown II"); Brown, D. J., "The Pyrimidines", in *The Chemistry of Heterocyclic Compounds, Volume 16, Supplement II* (Weissberger, A. and Taylor, E. C., Ed.), 1985, An Interscience Publication (John Wiley & Sons), New York ("Brown III"); Brown, D. J., "The Pyrimidines" in *The Chemistry of Heterocyclic Compounds, Volume 52* (Weissberger, A. and Taylor, E. C., Ed.), 1994, John Wiley & Sons, Inc., New York, pp. 1-1509 (Brown IV"); Kenner, G. W. and Todd, A., in *Heterocyclic Compounds*, Volume 6, (Elderfield, R. C., Ed.), 1957, John Wiley, New York, Chapter 7 (pyrimidines); Paquette, L. A., *Principles of Modern Heterocyclic Chemistry*, 1968, W. A. Benjamin, Inc., New York, pp. 1 – 401 (uracil synthesis pp. 313, 315; pyrimidine synthesis pp. 313-316; amino pyrimidine synthesis pp. 315); Joule, J. A., Mills, K. and Smith, G. F., *Heterocyclic Chemistry*, 3rd Edition, 1995, Chapman and Hall, London, UK, pp. 1 – 516; Vorbrüggen, H. and Ruh-Pohlenz, C., *Handbook of Nucleoside Synthesis*, John Wiley & Sons, New York, 2001, pp. 1-631 (protection of pyrimidines by acylation pp. 90-91; silylation of pyrimidines pp. 91-93); Joule, J. A., Mills, K. and Smith, G. F., *Heterocyclic Chemistry*, 4th Edition, 2000, Blackwell Science, Ltd, Oxford, UK, pp. 1 – 589; and *Comprehensive Organic Synthesis*, Volumes 1-9 (Trost, B. M. and Fleming, I., Ed.), 1991, Pergamon Press, Oxford, UK.

6.4 Inhibition of Fc Receptor Signal Cascades

Active 2,4-pyrimidinediamine compounds of the invention inhibit Fc receptor signalling cascades that lead to, among other things, degranulation of cells. As a specific example, the compounds inhibit the FcεRI and/or FcγRI signal cascades that lead to degranulation of immune cells such as neutrophil, eosinophil, mast and/or basophil cells. Both mast and basophil cells play a central role in allergen-induced disorders, ineluding, for example, allergie rhinitis and asthma. Referring to FIG. 1, upon exposure allergens, which may be, among other things, pollen or parasites, allergen-specific IgE antibodies are synthesized by B-cells activated by IL-4 (or IL-13) and other messengers to switch to IgE class specific antibody synthesis. These allergen-specific IgEs bind to the high affinity FcεRI. Upon binding of antigen, the FcεR1-bound IgEs are cross-linked and the IgE

receptor signal transduction pathway is activated, which leads to degranulation of the cells and consequent release and/or synthesis of a host of chemical mediators, including histamine, proteases (e.g., tryptase and chymase), lipid mediators such as leukotrienes (e.g., LTC4), platelet-activating factor (PAF) and prostaglandins (e.g., PGD2) and a series of cytokines, including TNF-α, IL-4, IL-13, IL-5, IL-6, IL-8, GMCSF, VEGF and TGF-β. The release and/or synthesis of these mediators from mast and/or basophil cells accounts for the early and late stage responses induced by allergens, and is directly linked to downstream events that lead to a sustained inflammatory state.

The molecular events in the FcεRI signal transduction pathway that lead to release of preformed mediators *via* degranulation and release and/or synthesis of other chemical mediators are well-known and are illustrated in FIG. 2. Referring to FIG. 2, the FcεRI is a heterotetrameric receptor composed of an IgE-binding alpha-subunit, a beta subunit, and two gamma subunits (gamma homodimer). Cross-linking of FcεRI-bound IgE by multivalent binding agents (including, for example IgE-specific allergens or anti-IgE antibodies or fragments) induces the rapid association and activation of the Src-related kinase Lyn. Lyn phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMS) on the intracellular beta and gamma subunits, which leads to the recruitment of additional Lyn to the beta subunit and Syk kinase to the gamma homodimer. These receptor-associated kinases, which are activated by intra- and intermolecular phosphorylation, phosphorylate other components of the pathway, such as the Btk kinase, LAT, and phospholipase C-gamma PLC-gamma). Activated PLC-gamma initiates pathways that lead to protein kinase C activation and Ca^{2+} mobilization, both of which are required for degranulation. FcεR1 cross-linking also activates the three major classes of mitogen activated protein (MAP) kinases, *i.e.* ERK1/2, JNK1/2, and p38. Activation of these pathways is important in the transcriptional regulation of proinflammatory mediators, such as TNF-α and IL-6, as well as the lipid mediator leukotriene CA (LTC4).

Although not illustrated, the FcγRI signaling cascade is believed to share some common elements with the FceRI signaling cascade. Importantly, like FcεRI, the FcγRI includes a gamma homodimer that is phosphorylated and recruits Syk, and like FcεRI, activation of the FcγRI signaling cascade leads to, among other things, degranulation. Other Fc receptors that share the gamma homodimer, and which can be regulated by the active 2,4-pyrimidinediamine compounds include, but are not limited to, FcαRI and FcγRIII.

The ability of the 2,4-pyrimidinediamine compounds of the invention to inhibit Fc receptor signaling cascades may be simply determined or confirmed in *in vitro* assays. Suitable assays for confirming inhition of FcεRI-mediated degranulation are provided in the Examples section. In one typical assay, cells capable of undergoing FcεRI-mediated degranulation, such as mast or basophil cells, are first grown in the presence of IL-4, Stem Cell Factor (SCF), IL-6 and IgE to increase expression of the FcεRI, exposed to a 2,4-pyrimidinediamine test compound of the invention and stimulated with anti-IgE antibodies (or, alternatively, an IgE-specific allergen). Following incubation, the amount of a chemical mediator or other chemical agent released and/or synthesized as a consequence of activating the FcεRI signaling cascade may be quantified using standard techniques and compared to the amount of the mediator or agent released from control cells (*i.e.*, cells that are stimulated but that are not exposed to test compound). The concentration of test compound that yields a 50% reduction in the quantity of the mediator or agent measured as compared to control cells is the IC_{50} of the test compound. The origin of the mast or basophil cells used in the assay will depend, in part, on the desired use for the compounds and will be apparent to those of skill in the art. For example, if the compounds will be used to treat or prevent a particular disease in humans, a convenient source of mast or basophil cells is a human or other animal which constitutes an accepted or known clinical model for the particular disease. Thus, depending upon the particular application, the mast or basophil cells may be derived from a wide variety of animal sources, ranging from, for example, lower mammals such as mice and rats, to dogs, sheep and other mammals commonly employed in clinical testing, to higher mammals such as monkeys, chimpanzees and apes, to humans. Specific examples of cells suitable for carrying out the *in vitro* assays include, but are not limited to, rodent or human basophil cells, rat basophil leukemia cell lines, primary mouse mast cells (such as bone marrow-derived mouse mast cells "BMMC") and primary human mast cells isolated from cord blood ("CHMC") or other tissues such as lung. Methods for isolating and culturing these cell types are well-known or are provided in the Examples section (*see, e.g.*, Demo *et al.*, 1999, Cytometry 36(4):340-348 and copending application Serial No. 10/053,355, filed November 8, 2001, the disclosures of which are incorporated herein by reference). Of course, other types of immune cells that degranulate upon activation of the FcεRI signaling cascade may also be used, including, for example, eosinophils.

As will be recognized by skilled artisans, the mediator or agent quantified is not critical. The only requirement is that it be a mediator or agent released and/or synthesized as a consequence of initiating or activating the Fc receptor signaling cascade. For example,

referring to FIG. 1, activation of the FcεRI signaling cascade in mast and/or basophil cells leads to numerous downstream events. For example, activation of the FcεRI signal cascade leads to the immediate release (i.e., within 1-3 min. following receptor activation) of a variety of preformed chemical mediators and agents *via* degranulation. Thus, in one embodiment, the mediator or agent quantified may be specific to granules (*i.e.,* present in granules but not in the cell cytoplasm generally). Examples of granule-specific mediators or agents that can be quantified to determine and/or confirm the activity of a 2,4-pyrimidinediamine compound of the invention include, but are not limited to, granule-specific enzymes such as hexosaminidase and tryptase and granule-specific components such as histamine and serotonin. Assays for quantifying such factors are well-known, and in many instances are commercially available. For example, tryptase and/or hexosaminidase release may be quantified by incubating the cells with cleavable substrates that fluoresce upon cleavage and quantifying the amount of fluorescence produced using conventional techniques. Such cleavable fluorogenic substrates are commercially available. For example, the fluorogenic substrates Z-Gly-Pro-Arg-AMC (Z=benzyloxycarbonyl; AMC=7-amino-4-methylcoumarin; BIOMOL Research Laboratories, Inc., Plymouth Meeting, PA 19462, Catalog No. P-142) and Z-Ala-Lys-Arg-AMC (Enzyme Systems Products, a division of ICN Biomedicals, Inc., Livermore, CA 94550, Catalog No. AMC-246) can be used to quantify the amount of tryptase released. The fluorogenic substrate 4-methylumbelliferyl-N-acetyl-β-D-glucosaminide (Sigma, St. Louis, MO, Catalog #69585) can be used to quantify the amount of hexosaminidase released. Histamine release may be quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) such as Immunotech histamine ELISA assay #IM2015 (Beckman-Coulter, Inc.). Specific methods of quantifying the release of tryptase, hexosaminidase and histamine are provided in the Examples section. Any of these assays may be used to determine or confirm the activity of the 2,4-pyrimidinediamine compounds of the invention.

Referring again to FIG. 1, degranulation is only one of several responses initiated by the FcεRI signaling cascade. In addition, activation of this signaling pathway leads to the *de novo* synthesis and release of cytokines and chemokines such as IL-4, IL-5, IL-6, TNF-α, IL-13 and MIP1-α), and release of lipid mediators such as leukotrienes (e.g., LTC4), platelet activating factor (PAF) and prostaglandins. Accordingly, the 2,4-pyrimidinediamine compounds of the invention may also be assessed for activity by

quantifying the amount of one or more of these mediators released and/or synthesized by activated cells.

Unlike the granule-specific components discussed above, these "late stage" mediators are not released immediately following activation of the FcεRI signaling cascade. Accordingly, when quantifying these late stage mediators, care should be taken to insure that the activated cell culture is incubated for a time sufficient to result in the synthesis (if necessary) and release of the mediator being quantified. Generally, PAF and lipid mediators such as leukotriene C4 are released 3-30 min. following FcεRI activation. The cytokines and other late stage mediators are released approx. 4-8 hrs. following FcεRI activation. Incubation times suitable for a specific mediator will be apparent to those of skill in the art. Specific guidance and assays are provided in the Examples section.

The amount of a particular late stage mediator released may be quantified using any standard technique. In one embodiment, the amount(s) may be quantified using ELISA assays. ELISA assay kits suitable for quantifying the amount of TNFα, IL-4, IL-5, IL-6 and/or IL-13 released are available from, for example, Biosource International, Inc., Camarillo, CA 93012 (see, e.g., Catalog Nos. KHC3011, KHC0042, KHC0052, KHC0061 and KHC0132). ELISA assay kits suitable for quantifying the amount of leukotriene C4 (LTC4) released from cells are available from Cayman Chemical Co., Ann Arbor, MI 48108 (see, e.g., Catalog No. 520211).

Typically, active 2,4-pyrimidinediamine compounds of the invention will exhibit IC_{50}s with respect to FcεRI-mediated degranulation and/or mediator release or synthesis of about 20 μM or lower, as measured in an *in vitro* assay, such as one of the *in vitro* assays described above or in the Examples section. Of course, skilled artisans will appreciate that compounds which exhibit lower IC_{50}s, for example on the order of 10 μM, 1 μM, 100 nM, 10 nM, 1 nM, or even lower, are particularly useful.

Skilled artisans will also appreciate that the various mediators discussed above may induce different adverse effects or exhibit different potencies with respect to the same adverse effect. For example, the lipid mediator LTC4 is a potent vasoconstrictor – it is approximately 1000-fold more potent at inducing vasoconstriction than histamine. As another example, in addition to mediating atopic or Type I hypersensitivity reactions, cytokines can also cause tissue remodeling and cell proliferation. Thus, although compounds that inhibit release and/or synthesis of any one of the previously discussed chemical mediators are useful, skilled artisans will appreciate that compounds which inhibit

the release and/or synthesis of a plurality, or even all, of the previously described mediators find particular use, as such compounds are useful for ameliorating or avoiding altogether a plurality, or even all, of the adverse effects induced by the particular mediators. For example, compounds whieh inhibit the release of all three types of mediators—granule-specific, lipid and cytokine—are useful for treating or preventing immediate Type I hypersensitivity reactions as well as the chronic symptoms associated therewith.

Compounds of the invention capable of inhibiting the release of more than one type of mediator (*e.g.*, granule-specific or late stage) may be identified by determining the IC_{50} with respect to a mediator representative of each class using the various *in vitro* assays described above (or other equivalent *in vitro* assays). Compounds of the invention which are capable of inhibiting the release of more than one mediator type will typically exhibit an IC_{50} for each mediator type tested of less than about 20 μM. For example, a compound which exhibits an IC_{50} of 1 μM with respect to histamine release ($IC_{50}^{histamine}$) and an IC_{50} of 1 nM with respect to leukotriene LTC4 synthesis and/or release (IC_{50}^{LTC4}) inhibits both immediate (granule-specific) and late stage mediator release. As another specific example, a compound that exhibits an $IC_{50}^{tryptase}$ of 10 μM, an IC_{50}^{LTC4} of 1 μM and an IC_{50}^{IL-4} of 1 μM inhibits immediate (granule-specific), lipid and cytokine mediator release. Although the above specific examples utilize the IC_{50}s of one representative mediator of each class, skilled artisans will appreciate that the IC_{50}s of a plurality, or even all, mediators comprising one or more of the classes may be obtained. The quantity(ies) and identity(ies) of mediators for which IC_{50} data should be ascertained for a particular compound and application will be apparent to those of skill in the art.

Similar assays may be utilized to confirm inhibition of signal transduction eascades initiated by other Fc receptors, such as FcαRI, FcγRI and/or FcγRIII signaling, with routine modification. For example, the ability of the compounds to inhibit FcγRI signal transduction may be confirmed in assays similar to those described above, with the exeeption that the FcγRI signaling cascade is activated, for example by incubating the cells with IgG and an IgG-specific allergen or antibody, instead of IgE and an IgE-specific allergen or antibody. Suitable cell types, activating agents and agents to quantify to confirm inhibition of other Fc receptors, such as Fc receptors that comprise a gamma homodimer, will be apparent to those of skill in the art.

One particularly useful class of compounds includes those 2,4-pyrimidinediamine compounds that inhibit the release of immediate granule-specific mediators and late stage

mediators with approximately equivalent IC_{50}s. By approximately equivalent is meant that the IC_{50}s for each mediator type are within about a 10-fold range of one another. Another particularly useful class of compounds includes those 2,4-pyrimidinediamine compounds that inhibit the release of immediate granule-specific mediators, lipid mediators and cytokine mediators with approximately equivalent IC_{50}s. In a specific embodiment, such compounds inhibit the release of the following mediators with approximately equivalent IC_{50}s: histamine, tryptase, hexosaminidase, IL-4, IL-5, IL-6, IL-13, TNFα and LTC4. Such compounds are particularly useful for, among other things, ameliorating or avoiding altogether both the early and late stage responses associated with atopic or immediate Type I hypersensitivity reactions.

Ideally, the ability to inhibit the release of all desired types of mediators will reside in a single compound. However, mixtures of compounds can also be identified that achieve the same result. For example, a first compound which inhibits the release of granule specific mediators may be used in combination with a second compound which inhibits the release and/or synthesis of cytokine mediators.

In addition to the FcεRI or FcγRI degranulation pathways discussed above, degranulation of mast and/or basophil cells can be induced by other agents. For example, ionomycin, a calcium ionophore that bypasses the early FcεRI or FcγRI signal transduction machinery of the cell, directly induces a calcium flux that triggers degranulation. Referring again to FIG. 2, activated PLCγ initiates pathways that lead to, among other things, calcium ion mobilization and subsequent degranulation. As illustrated, this Ca^{2+} mobilization is triggered late in the FcεRI signal transduction pathway. As mentioned above, and as illustrated in FIG. 3, ionomycin directly induces Ca^{2+} mobilization and a Ca^{2+} flux that leads to degranulation. Other ionophores that induce degranulation in this manner include A23187. The ability of granulation-inducing ionophores such as ionomycin to bypass the early stages of the FcεRI and/or FcγRI signaling cascades may be used as a counter screen to identify active compounds of the invention that specifically exert their degranulation-inhibitory activity by blocking or inhibiting the early FcεRI or FcγRI signaling cascades, as discussed above. Compounds which specifically inhibit such early FcεRI or FcγRI-mediated degranulation inhibit not only degranulation and subsequent rapid release of histamine, tryptase and other granule contents, but also inhibit the pro-inflammatory activation pathways causing the release of TNFα, IL-4, IL-13 and the lipid mediators such as LTC4. Thus, compounds which specifically inhibit such early FcεRI and/or FcγRI-

mediated degranulation block or inhibit not only acute atopic or Type I hypersensitivity reactions, but also late responses involving multiple inflammatory mediators.

Compounds of the invention that specifically inhibit early FcεRI and/or FcγRI-mediated degranulation are those compounds that inhibit FcεRI and/or FcγRI-mediated degranulation (for example, have an IC_{50} of less than about 20 μM with respect to the release of a granule-specific mediator or component as measured in an *in vitro* assay with cells stimulated with an IgE or IgG binding agent) but that do not appreciably inhibit ionophore-induced degranulation. In one embodiment, compounds are considered to not appreciably inhibit ionophore-induced degranulation if they exhibit an IC_{50} of ionophore-induced degranulation of greater than about 20 μM, as measured in an *in vitro* assay. Of course, active compounds that exhibit even higher IC_{50}s of ionophore-induced degranulation, or that do not inhibit ionophore-induced degranulation at all, are particularly useful. In another embodiment, compounds are considered to not appreciably inhibit ionophore-induced degranulation if they exhibit a greater than 10-fold difference in their IC_{50}s of FcεRI and/or FcγRI-mediated degranulation and ionophore-induced degranulation, as measured in an *in vitro* assay. Assays suitable for determining the IC_{50} of ionophore-induced degranulation include any of the previously-described degranulation assays, with the modification that the cells are stimulated or activated with a degranulation-inducing calcium ionophore such as ionomycin or A23187 (A.G. Scientific, San Diego, CA) instead of anti-IgE antibodies or an IgE-specific allergen. Specific assays for assessing the ability of a particular 2,4-pyrimidinediamine compound of the invention to inhibit ionophore-induced degranulation are provided in the Examples section.

As will be recognized by skilled artisans, compounds which exhibit a high degree of selectivity of FcεRI-mediated degranulation find particular use, as such compounds selectively target the FcεRI cascade and do not interfere with other degranulation mechanisms. Similarly, compounds which exhibit a high degree of selectivity of FcγRI-mediated degranulation find particular use, as such compounds selectively target the FcγRI cascade and do not interfere with other degranulation mechanisms. Compounds which exhibit a high degree of selectivity are generally 10-fold or more selective for FcεRI- or FcγRI -mediated degranulation over ionophore-induced degranulation, such as ionomycin-induced degranulation.

Biochemieal and other data confirm that the 2,4-pyrimidinediamine compounds described herein are potent inhibitors of Syk kinase activity. For example, in experiments

with an isolated Syk kinase, of twenty four 2,4-pyrimidinediamine compounds tested, all but two inhibited the Syk kinase catalyzed phosphorylation of a peptide substrate with IC50s in the submicromolar range. The remaining compounds inhibited phosphorylation in the micromolar range. In addition, of sixteen compounds tested in an *in vitro* assay with mast cells, all inhibited phosphorylation of Syk kinase substrates (*e.g.*, PLC-gamma1, LAT) and proteins downstream of Syk kinase (*e.g.*, JNK, p38, Erk1/2 and PKB, when tested), but not proteins upstream of Syk kinase in the cascade (*e.g.*, Lyn). Phosphorylation of Lyn substrates was not inhibited by the 2,4-pyrimidinediamine compounds tested. Moreover, for the following compounds, a high correlation was observed between their inhibition of Syk kinase activity in biochemical assays (IC_{50}s in the range of 3 to 1850 nM) and their inhibition of FcεR1-mediated degranulation in mast cells (IC_{50}s in the range of 30 to 1650 nM): R950373, R950368, R921302, R945371, R945370, R945369, R945365, R921304, R945144, R945140, R945071, R940358, R940353, R940352, R940351, R940350, R940347, R921303, R940338, R940323, R940290, R940277, R940276, R940275, R940269, R940255, R935393, R935372, R935366, R935310, R935309, R935307, R935304, R935302, R935293, R935237, R935198, R935196, R935194, R935193, R935191, R935190, R935138, R927050, R926968, R926956, R926931, R926891, R926839, R926834, R926816, R926813, R926791, R926782, R926780, R926757, R926753, R926745, R926715, R926508, R926505, R926502, R926501, R926500, R921218, R921147, R920410, R909268, R921219, R908712, R908702.

Accordingly, the activity of the 2,4-pyrimidinediamine compounds of the invention may also be confirmed in biochemical or cellular assays of Syk kinase activity. Referring again to FIG. 2, in the FcεRI signaling cascade in mast and/or basophil cells, Syk kinase phosphorylates LAT and PLC-gamma1, which leads to, among other things, degranulation. Any of these activities may be used to confirm the activity of the 2,4-pyrimidinediamine compounds of the invention. In one embodiment, the activity is confirmed by contacting an isolated Syk kinase, or an active fragment thereof with a 2,4-pyrimidinediamine compound in the presence of a Syk kinase substrate (*e.g.*, a synthetic peptide or a protein that is known to be phophorylated by Syk in a signaling cascade) and assessing whether the Syk kinase phosphorylated the substrate. Alternatively, the assay may be carried out with cells that express a Syk kinase. The cells may express the Syk kinase endogenously or they may be engineered to express a recombinant Syk kinase. The cells may optionally also express the Syk kinase substrate. Cells suitable for performing sueh confirmation assays, as well as methods of engineering suitable cells will be apparent to those of skill in the art. Specific

examples of biochemical and cellular assays suitable for confirming the activity of the 2,4-pyrimidinediamine compounds are provided in the Examples section.

Generally, eompounds that are Syk kinase inhibitors will exhibit an IC_{50} with respect to a Syk kinase activity, such as the ability of Syk kinase to phosphorylate a synthetic or endogenous substrate, in an *in vitro* or cellular assay in the range of about 20 μM or less. Skilled artisans will appreciate that compounds that exhibit lower IC50s, such as in the range of 10 μM, 1μM, 100 nM, 10 nM, 1 nM, or even lower, are particularly useful.

6.5 Uses and Compositions

As previously discussed, the active compounds of the invention inhibit Fc receptor signaling cascades, especially those Fc receptors including a gamma homodimer, such as the FcϵRI and/or FcγRI signaling cascades, that lead to, among other things, the release and/or synthesis of chemical mediators from cells, either *via* degranulation or other processes. As also discussed, the active compounds are also potent inhibitors of Syk kinase. As a consequence of these activities, the active compounds of the invention may be used in a variety of *in vitro, in vivo* and *ex vivo* contexts to regulate or inhibit Syk kinase, signaling cascades in which Syk kinase plays a role, Fc receptor signaling cascades, and the biological responses effected by such signaling cascades. For example, in one embodiment, the compounds may be used to inhibit Syk kinase, either *in vitro* or *in vivo*, in virtually any cell type expressing Syk kinase. They may also be used to regulate signal transduction cascades in which Syk kinase plays a role. Such Syk-dependent signal transduction cascades include, but are not limited to, the FcϵRI, FcγRI, FcγRIII, BCR and integrin signal transduction cascades. The compounds may also be used *in vitro* or *in vivo* to regulate, and in particular inhibit, cellular or biological responses effected by such Syk-dependent signal transduction cascades. Such cellular or biological responses include, but are not limited to, respiratory burst, cellular adhesion, cellular degranulation, cell spreading, cell migration, cell aggregation, phagcytosis, cytokine synthesis and release, cell maturation and Ca^{2+} flux. Importantly, the compounds may be used to inhibit Syk kinase *in vivo* as a therapeutic approach towards the treatment or prevention of diseases mediated, either wholly or in part, by a Syk kinase activity. Non-limiting examples of Syk kinase mediated diseases that may be treated or prevented with the compounds are those discussed in more detail, below.

In another embodiment, the active compounds may be used to regulate or inhibit the Fc receptor signaling cascades and/or FcϵRI- and/or FcγRI-mediated degranulation as a therapeutic approach towards the treatment or prevention of diseases characterized by,

caused by and/or associated with the release or synthesis of chemical mediators of such Fc receptor signaling cascades or degranulation. Such treatments may be administered to animals in veterinary contexts or to humans. Diseases that are characterized by, caused by or associated with such mediator release, synthesis or degranulation, and that can therefore be treated or prevented with the active compounds include, by way of example and not limitation, atopy or anaphylactic hypersensitivity or allergic reactions, allergies (e.g., allergic conjunctivitis, allergic rhinitis, atopic asthma, atopic dermatitis and food allergies), low grade scarring (*e.g.*, of scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury and post myocardial infarction), diseases associated with tissue destruction (*e.g.*, of COPD, cardiobronchitis and post myocardial infarction), diseases associated with tissue inflammation (*e.g.*, irritable bowel syndrome, spastic colon and inflammatory bowel disease), inflammation and scarring.

When used to treat or prevent such diseases, the active compounds may be administered singly, as mixtures of one or more active compounds or in mixture or combination with other agents useful for treating such diseases and/or the symptoms associated with such diseases. The active compounds may also be administered in mixture or in combination with agents useful to treat other disorders or maladies, such as steroids, membrane stablizers, 5LO inhibitors, leukotriene synthesis and receptor inhibitors, inhibitors of IgE isotype switching or IgE synthesis, IgG isotype switching or IgG synthesis, β-agonists, tryptase inhibitors, aspirin, COX inhibitors, methotrexate, anti-TNF drugs, retuxin, PD4 inhibitors, p38 inhibitors, PDE4 inhibitors, and antihistamines, to name a few. The active compounds may be administered *per se* in the form of prodrugs or as pharmaceutical compositions, comprising an active compound or prodrug.

Pharmaceutical compositions comprising the active compounds of the invention (or prodrugs thereof) may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making levigating, emulsifying, encapsulating, entrapping or lyophilization processes. The compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically.

The active compound or prodrug may be formulated in the pharmaceutical compositions *per se*, or in the form of a hydrate, solvate, N-oxide or pharmaceutically

acceptable salt, as previously described. Typically, such salts are more soluble in aqueous solutions than the corresponding free acids and bases, but salts having lower solubility than the corresponding free acids and bases may also be formed.

Pharmaceutical compositions of the invention may take a form suitable for virtually any mode of administration, including, for example, topical, ocular, oral, buccal, systemic, nasal, injection, transdermal, rectal, vaginal, etc., or a form suitable for administration by inhalation or insufflation.

For topical administration, the active compound(s) or prodrug(s) may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

Systemic formulations include those designed for administration by injection, *e.g.*, subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

Useful injectable preparations include sterile suspensions, solutions or emulsions of the active compound(s) in aqueous or oily vehicles. The compositions may also contain formulating agents, such as suspending, stabilizing and/or dispersing agent. The formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, and may contain added preservatives.

Alternatively, the injectable formulation may be provided in powder form for reconstitution with a suitable vehicle, including but not limited to sterile pyrogen free water, buffer, dextrose solution, etc., before use. To this end, the active compound(s) may be dried by any art-known technique, such as lyophilization, and reconstituted prior to use.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are known in the art.

For oral administration, the pharmaceutical compositions may take the form of, for example, lozenges, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). The tablets may be coated by methods well known in the art with, for example, sugars, films or enteric coatings. Compounds which are particularly suitable for oral administration include Compounds R940350, R935372, R935193, R927050 and R935391.

Liquid preparations for oral administration may take the form of, for example, elixirs, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol, cremophore™ or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, preservatives, flavoring, coloring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound or prodrug, as is well known.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For rectal and vaginal routes of administration, the active compound(s) may be formulated as solutions (for retention enemas) suppositories or ointments containing conventional suppository bases such as cocoa butter or other glycerides.

For nasal administration or administration by inhalation or insufflation, the active compound(s) or prodrug(s) can be conveniently delivered in the form of an aerosol spray from pressurized packs or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, fluorocarbons, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges for use in an inhaler or insufflator (for example capsules and cartridges comprised of gelatin) may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

A specific example of an aqueous suspension formulation suitable for nasal administration using commercially-available nasal spray devices includes the following ingredients: active compound or prodrug (0.5-20 mg/ml); benzalkonium chloride (0.1-0.2 mg/mL); polysorbate 80 (TWEEN® 80; 0.5-5 mg/ml); carboxymethylcellulose sodium or microcrystalline cellulose (1-15 mg/ml); phenylethanol (1-4 mg/ml); and dextrose (20-50 mg/ml). The pH of the final suspension can be adjusted to range from about pH5 to pH7, with a pH of about pH 5.5 being typical.

Another specific example of an aqueous suspension suitable for administration of the compounds *via* inhalation, and in particular for such administration of Compound

R921218, contains 1-20 mg/mL Compound or prodrug, 0.1-1% (v/v) Polysorbate 80 (TWEEN®80), 50 mM citrate and/or 0.9% sodium chloride.

For ocular administration, the active compound(s) or prodrug(s) may be formulated as a solution, emulsion, suspension, etc. suitable for administration to the eye. A variety of vehicles suitable for administering compounds to the eye are known in the art. Specific non-limiting examples are described in U.S. Patent No. 6,261,547; U.S. Patent No. 6,197,934; U.S. Patent No. 6,056,950; U.S. Patent No. 5,800,807; U.S. Patent No. 5,776,445; U.S. Patent No. 5,698,219; U.S. Patent No. 5,521,222; U.S. Patent No. 5,403,841; U.S. Patent No. 5,077,033; U.S. Patent No. 4,882,150; and U.S. Patent No. 4,738,851.

For prolonged delivery, the active compound(s) or prodrug(s) can be formulated as a depot preparation for administration by implantation or intramuscular injection. The active ingredient may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, e.g., as a sparingly soluble salt. Alternatively, transdermal delivery systems manufactured as an adhesive disc or patch which slowly releases the active compound(s) for percutaneous absorption may be used. To this end, permeation enhancers may be used to facilitate transdermal penetration of the active compound(s). Suitable transdermal patches are described in for example, U.S. Patent No. 5,407,713.; U.S. Patent No. 5,352,456; U.S. Patent No. 5,332,213; U.S. Patent No. 5,336,168; U.S. Patent No. 5,290,561; U.S. Patent No. 5,254,346; U.S. Patent No. 5,164,189; U.S. Patent No. 5,163,899; U.S. Patent No. 5,088,977; U.S. Patent No. 5,087,240; U.S. Patent No. 5,008,110; and U.S. Patent No. 4,921,475.

Alternatively, other pharmaceutical delivery systems may be employed. Liposomes and emulsions are well-known examples of delivery vehicles that may be used to deliver active compound(s) or prodrug(s). Certain organic solvents such as dimethylsulfoxide (DMSO) may also be employed, although usually at the cost of greater toxicity.

The pharmaceutical compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active compound(s). The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

6.6 Effective Dosages

The active compound(s) or prodrug(s) of the invention, or compositions thereof, will generally be used in an amount effective to achieve the intended result, for example in an amount effective to treat or prevent the particular disease being treated. The compound(s) may be administered therapeutically to achieve therapeutic benefit or prophylactically to achieve prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted with the underlying disorder. For example, administration of a compound to a patient suffering from an allergy provides therapeutic benefit not only when the underlying allergic response is eradicated or ameliorated, but also when the patient reports a decrease in the severity or duration of the symptoms associated with the allergy following exposure to the allergen. As another example, therapeutic benefit in the context of asthma includes an improvement in respiration following the onset of an asthmatic attack, or a reduction in the frequency or severity of asthmatic episodes. Therapeutic benefit also includes halting or slowing the progression of the disease, regardless of whether improvement is realized.

For prophylactic administration, the compound may be administered to a patient at risk of developing one of the previously described diseases. For example, if it is unknown whether a patient is allergic to a particular drug, the compound may be administered prior to administration of the drug to avoid or ameliorate an allergic response to the drug. Alternatively, prophylactic administration may be applied to avoid the onset of symptoms in a patient diagnosed with the underlying disorder. For example, a compound may be administered to an allergy sufferer prior to expected exposure to the allergen. Compounds may also be administered prophylactically to healthy individuals who are repeatedly exposed to agents known to one of the above-described maladies to prevent the onset of the disorder. For example, a compound may be administered to a healthy individual who is repeatedly exposed to an allergen known to induce allergies, such as latex, in an effort to prevent the individual from developing an allergy. Alternatively, a compound may be administered to a patient suffering from asthma prior to partaking in activities which trigger asthma attacks to lessen the severity of, or avoid altogether, an asthmatie episode.

The amount of compound administered will depend upon a variety of factors, including, for example, the particular indication being treated, the mode of administration,

whether the desired benefit is prophylactic or therapeutic, the severity of the indication being treated and the age and weight of the patient, the bioavailability of the particular active eompound, etc. Determination of an effective dosage is well within the capabilities of those skilled in the art.

Effective dosages may be estimated initially from *in vitro* assays. For example, an initial dosage for use in animals may be formulated to achieve a circulating blood or serum concentration of active compound that is at or above an IC_{50} of the particular compound as measured in as *in vitro* assay, such as the *in vitro* CHMC or BMMC and other *in vitro* assays described in the Examples section. Calculating dosages to achieve such circulating blood or serum concentrations taking into account the bioavailability of the particular compound is well within the capabilities of skilled artisans. For guidance, the reader is referred to Fingl & Woodbury, "General Principles," *In: Goodman and Gilman's The Pharmaceutical Basis of Therapeutics*, Chapter 1, pp. 1-46, latest edition, Pagamonon Press, and the references cited therein.

Initial dosages can also be estimated from *in vivo* data, such as animal models. Animal models useful for testing the efficacy of compounds to treat or prevent the various diseases described above are well-known in the art. Suitable animal modcls of hypersensitivity or allergic reactions are described in Foster, 1995, Allergy 50(21Suppl):6-9, discussion 34-38 and Tumas *et al.*, 2001, J. Allergy Clin. Immunol. 107(6):1025-1033. Suitable animal models of allergic rhinitis are described in Szelenyi *et al.*, 2000, Arzneimittelforschung 50(11):1037-42; Kawaguchi *et al.*, 1994, Clin. Exp. Allergy 24(3):238-244 and Sugimoto *et al.*, 2000, Immunopharmacology 48(1):1-7. Suitable animal models of allergic conjunctivitis are described in Carreras *et al.*, 1993, Br. J. Ophthalmol. 77(8):509-514; Saiga *et al.*, 1992, Ophthalmic Res. 24(1):45-50; and Kunert *et al.*, 2001, Invest. Ophthalmol. Vis. Sci. 42(11):2483-2489. Suitable animal models of systemic mastocytosis are described in O'Keefe *et al.*, 1987, J. Vet. Intern. Med. 1(2):75-80 and Bean-Knudsen *et al.*, 1989, Vet. Pathol. 26(1):90-92. Suitable animal models of hyper IgE syndrome are described in Claman *et al.*, 1990, Clin. Immunol. Immunopathol. 56(1):46-53. Suitable animal models of B-cell lymphoma are described in Hough *et al.*, 1998, Proc. Natl. Acad. Sci. USA 95:13853-13858 and Hakim *et al.*, 1996, J. Immunol. 157(12):5503-5511. Suitable animal models of atopic disorders such as atopic dermatitis, atopic eczema and atopic asthma are described in Chan *et al.*, 2001, J. Invest. Dermatol. 117(4):977-983 and Suto *et al.*, 1999, Int. Arch. Allergy Immunol. 120(Suppl 1):70-75. Ordinarily skilled

artisans can routinely adapt such information to determine dosages suitable for human administration. Additional suitable animal models are described in the Examples section.

Dosage amounts will typically be in the range of from about 0.0001 or 0.001 or 0.01 mg/kg/day to about 100 mg/kg/day, but may be higher or lower, depending upon, among other factors, the activity of the compound, its bioavailability, the mode of administration and various factors discussed above. Dosage amount and interval may be adjusted individually to provide plasma levels of the compound(s) which are sufficient to maintain therapeutic or prophylactic effect. For example, the compounds may be administered once per week, several times per week (e.g., every other day), once per day or multiple times per day, depending upon, among other things, the mode of administration, the specific indication being treated and the judgment of the prescribing physician. In cases of local administration or selective uptake, such as local topical administration, the effective local concentration of active compound(s) may not be related to plasma concentration. Skilled artisans will be able to optimize effective local dosages without undue experimentation.

Preferably, the compound(s) will provide therapeutic or prophylactic benefit without causing substantial toxicity. Toxicity of the compound(s) may be determined using standard pharmaceutical procedures. The dose ratio between toxic and therapeutic (or prophylactic) effect is the therapeutic index. Compounds(s) that exhibit high therapeutic indices are preferred.

The invention having been described, the following examples are offered by way of illustration and not limitation.

7. EXAMPLES

7.1 Synthesis of Starting Materials and Intermediates Useful for Synthesizing The 2,4-Pyrimidinediamine Compounds According to Schemes (I)–(V)

A variety of starting materials and N4-monosubstituted-2-pyrimidineamines and N2-monosubstituted-4-pyrimidinediamines [mono Substitution Nucleophilic Aromatic Reaction (SNAR) products] useful for synthesizing the 2,4-pyrimidinediamine compounds of the invention according to Schemes (I)-(V) were prepared as described below. Conditions suitable for synthesizing the mono SNAR products are exemplified with 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (**R926087**).

7.1.1 2,4-Dichloro-5-fluoropyrimidine

To a dry reaction flask equipped with a stir bar and a reflux condenser was placed 5-fluorouracil (0.65g, 5mmol) followed by phosphorus oxychloride ($POCl_3$) (1.53g, 10mmol). The resultant mixture was heated at 110 °C for 8 hours under a nitrogen atmosphere. The reaction was cooled to room temperature, phosphorus pentachloride (PCl_5) (3.12g, 15mmol) was added and heated to 110 °C for a period of 12 hours. After cooling to room temperature, the mixture was poured into ice-water, saturated with sodium chloride and left for 1 hour at 0 °C to complete the decomposition of $POCl_3$ and PCl_5. The solid of 2,4-dichloro-5-fluoropyrimidine was collected by rapid filtration, dried using blotting paper and stored at low temperature. ^1H NMR ($CDCl_3$): δ 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 155.42, 151.87, 147.43 and 147.13; ^{19}F NMR ($CDCl_3$): – 38149.

7.1.2 2,4-Dichloro-5-nitropyrimidine (Aldrich D6, 930-0)

A suspension of 5-nitrouracil (10g, 63 mmol) in $POCl_3$ (100 mL) was refluxed for 5h in the presence of N,N-dimethylaniline (10 mL), cooled to room temperature and poured on to crushed ice with vigorous stirring. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduce pressure. The residue was purified by chromatography on silica gel (hexane/ethyl acetate; 1/1; v/v) to give the desired 2,4-dichloro-5-nitropyrimidine. LCMS: ret. time: 23.26 min.; purity: 95%; ^1H NMR ($CDCl_3$): δ 9.16 (1H, s).

7.1.3 2,4-Dichloro-5-cyanopyrimidine

In like manner to the preparation of 2,4-dichloro-5-nitropyrimidine, the reaction of 5-cyanouracil with $POCl_3$ and N,N-dimethylaniline gave 2,4-dichloro-5-cyanopyrimidine. LCMS: ret. time: 13.75 min.; purity: 95%.

7.1.4 2,4-Dichloro-5-trifluoromethylpyrimidine

In like manner to the preparation of 2,4-dichloro-5-nitropyrimidine, the reaction of 5-cyanouracil with $POCl_3$ and N,N-dimethylaniline gave 2,4-dichloro-5-cyanopyrimidine. ^1H NMR (CD_3OD): δ 9.07; LCMS: ret. time: 16.98 min. (fast method); purity: 70%.

7.1.5 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (R926087)

The reaction flask equipped with a magnetic stirring bar and a rubber septum (to prevent loss of 2,4-dichloro-5-fluoropyrimidine and N_2 inlet was eharged with 3,4-ethylenedioxyaniline (34 g, 225 mmol), MeOH (100 mL), H_2O (300 mL) and 2,4-dichloro-5-fluoropyrimidine (25 g, 150 mmol). The reaction mixture was stirred at room temperature for 1h, diluted with H_2O (1.5 liter), acidified with 2N HCl (200 mL) and sonicated. The solid obtained was filtered, washed with H_2O and dried to obtain 33 g (78%) of the desired product, 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine **(R926087).** ^1H NMR ($CDCl_3$): δ 8.02 (1H, d, J= 3Hz), 7.25 (d, 1H, J= 1.2 Hz), 6.98 (dd, 1H, J= 2.4 and 8.1 Hz), 6.85 (d, 1H, J= 5.7 Hz), 4.27 (m, 4H); ^{19}F NMR ($CDCl_3$): - 44570; LCMS: ret. time: 26.70 min.; purity 100%; MS (m/e): 283 (MH^+).

7.1.6 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-nitro-4-pyrimidineamine (R940094)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-nitropyrimidine and 3,4-ethylenedioxyaniline were reacted to prepare 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-nitro-4-pyrimidineamine. LCMS: ret. time: 28.79 min.; purity: 90%; MS (m/e): 308 (M^+); ^{1}HNMR ($CDCl_3$): δ 10.07 (1H, s), 9.15 (1H, s), 7.02-6.88 (3H, m), 4.29 (4H, s).

7.1.7 2-Chloro-N4-(3-hydroxyphenyl)-5-nitro-4-pyrimidineamine (R940097)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-nitropyrimidine and 3-hydroxyaniline were reacted to prepare 2-chloro-N4-(3-hydroxyphenyl)-5-nitro-4-pyrimidineamine. LCMS: ret. time: 24.21 min.; purity: 93%; MS (m/e): 267 (MH^+); ^{1}HNMR ($CDCl_3$): δ 10.20 (1H, s), 9.19 (1H, s), 7.32 (1H, t, J= 2.2 Hz), 7.28 (1H, d, J= 7.8 Hz), 7.11 (1H, dd, J= 7.8 and 1.8 Hz), 7.76 (1H, dd, J= 8.4 and 2.4 Hz), 5.20 (1H, s).

7.1.8 2-Chloro-N4-(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (R926111)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxyaniline were reacted to prepare product 2-chloro-N4-(3-hydroxyphenyl)-5-fluoro-4-pyrimidineamine. ^1H

NMR (CD_3OD): δ 8.06 (bd, 1H), 7.26 (bd, 1H), 7.20-7.00 (m, 2H), 6,57 (d, 1H, J= 7.2 Hz); ^{19}F NMR (CD_3OD): - 44374; LCMS: ret. time: 22.02; purity: 100%, MS (m/e): 240 (M^+).

7.1.9 2-Chloro-N4-(3,4-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine (R926073)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-dimethoxyaniline were reacted to prepare 2-chloro-N4-(3,4-dimethoxyphenyl)-5-fluoro-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 8.02 (d, 1H, J= 2.7 Hz), 7.38 (d, 1H, J= 2.4 Hz), 7.05 (dd, 1H, J= 2.4 and 9.0 Hz), 6.89 (bs, 1H), 6.88 (d, 1H, J= 9 Hz), 3.91 (s, 3H), 3.89 (s, 3H); ^{19}F NMR ($CDCl_3$): - 44593; LCMS: ret. time: 24.95 min.; purity: 98%; MS (m/e): 285 (MH^+).

7.1.10 2-Chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine (R926066)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-ethoxyaniline were reacted to prepare 2-chloro-N4-(4-ethoxyphenyl)-5-fluoro-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 8.01 (d, 1H, J= 3Hz), 7.49 (bdd, 2H, J= 8.7 Hz), 6.92 (bdd, 2H, J= 9.6 Hz), 4.03 (q, 2H, J= 7.2 Hz), 1.42 (t, 3H, J= 7.2 Hz); ^{19}F NMR ($CDCl_3$): - 44627; LCMS: ret. time: 29.50 min.; purity: 99%, MS (m/e): 268 (MH^+).

7.1.11 2-Chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine (R926207)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloroaniline were reacted to prepare 2-chloro-N4-(4-chlorophenyl)-5-fluoro-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 8.1 (bs, 1H), 8.60 (bdd, 2H), 8.36 (bdd, 2H), 6.90 (bs, 1H); ^{19}F NMR ($CDCl_3$): - 44407; LCMS: ret. time: 31.63 min.; purity: 85%; MS (m/e): 258 (MH^+).

7.1.12 2-Chloro-5-fluoro-N4-(3-hydroxy-4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine (R926393)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methoxycarbonylmethylenoxyaniline were reacted to prepare 2-chloro-5-fluoro-N4-(3-hydroxy-4-methoxycarbonylmethyleneoxyphenyl)-4-pyrimidineamine. ^1H NMR (CD_3OD):

δ 8.03 (d, 1H, J= 3.6 Hz), 7.35 (dd, 1H, J= 2.4 Hz), 7.12 (dd, 1H, J= 2.4 and 8.7 Hz), 6.82 (d, 1H, J= 8.1 Hz), 4.86 (s, 2H), 3.81 (s, 3H).

7.1.13 N4-(4-tert-Butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R926573)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and tert-butyl 4-aminophenoxyacetate were reacted to prepare product N4-(4-tert-butoxycarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.02 (d, 1H, J= 2.7 Hz), 7.51 (d, 1H, J= 8.7 Hz), 6.93 (d, 1H, J= 8.7 Hz), 4.52 (s, 2H)), 1.49 (s, 9H); LCMS: ret. time: 29.50 min.; purity: 97%; MS (m/e): 354 (MH^+).

7.1.14 2-Chloro-5-fluoro-N4-(indol-5-yl)-4-pyrimidineamine (R926581)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-aminoindole were reacted to prepare 2-chloro-5-fluoro-N4-(indol-5-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 9.45 (bs, 1H), 8.00 (bs, 1H), 7.82 (bd, 1H), 7.75 (s, 1H), 7.38-7.10 (m, 3H), 6.40 (bs, 1H); LCMS: ret. time: 23.85 min.; purity: 100%; MS (m/e): 263 (MH^+).

7.1.15 2-Chloro-5-fluoro-N4-(4-methoxymethyl-coumarin-7-yl)-4-pyrimidineamine (R926618)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-methoxymethyl-7-aminocoumarin were reacted to prepare 2-chloro-5-fluoro-N4-(4-methoxymethyl-coumarin-7-yl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.05 (d, 1H), 7.90 (s, 1H), 7.70 (dd, 1H, J= 2.4 and 8.7 Hz), 7.53 (d, 1H, J= 8.7 Hz), 6.42 (s, 1H), 4.61 (s, 2H), 3.49 (s, 3H); LCMS: ret. time: 26.38 min.; purity: 87%; MS (m/e): 336 (MH^+).

7.1.16 2-Chloro-N4-(2,5-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (R926619)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2,5-dimethyl-4-hydroxyaniline were reacted to prepare 2-chloro-N4-(2,5-dimethyl-4-hydroxyphenyl)-5-

fluoro-4-pyrimidineamine. LCMS: ret. time: 23.31 min.; purity: 96%; MS (m/e): 268 (MH^+).

7.1.17 2-Chloro-N4-(5-chloropyrid-2-yl)-5-fluoro-4-pyrimidineamine (R926061)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-chloro-2-aminopyridine were reacted to prepare 2-chloro-N4-(5-chloropyrid-2-yl)-5-fluoro-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 8.40 (d, 1H, J= 8.7 Hz), 8.28 (d, 1H, J= 1.8 Hz), 8.17 (d, 1H, J= 2.1 and 9 Hz); LCMS: ret. time: 28.58 min.; purity: 100%; MS (m/e): 259 (MH^+).

7.1.18 2-Chloro-5-fluoro-N4-(5-methylpyrid-2-yl))-4-pyrimidineamine (R926062)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-methyl-2-aminopyridine were reacted to prepare 2-chloro-5-fluoro-N4-(5-methylpyrid-2-yl)-5-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 9.20 (s, 1H), 8.51 (s, 1H), 7.63 (d, 1H, J= 5.7 Hz), 7.45 (dd, 1H, J= 1.8 and 9.3 Hz), 2.43 (s, 3H); LCMS: ret. time: 21.29 min.; purity: 97%; MS (m/e): 239 (MH^+).

7.1.19 N4-[6-(1,4-Benzoxazinyl)]-N2-chloro-5-fluoro-4-pyrimidineamine

In like manner to 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-1,4-benzoxazine were reacted (in methanol or methanol:water) to yield N4-[6-(1,4-benzoxazinyl)]-N2-chloro-5-fluoro-4-pyrimidineamine. ^1H NMR (DMSO-d6): δ 8.2 (d, 1H), 6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H); LCMS: ret. time: 20.8 min.; purity: 95 %; MS (m/e): 295 (MH^+).

7.1.20 N2-Chloro-N4-(2,3-dihydrobenzofuran-5-yl)-5-fluoro-4-pyrimidinediamine

In like manner to 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-2,3-dihydrobenzofuran were reacted to yield N2-chloro-N4-(2,3-dihydrobenzofuran-5-yl)-5-fluoro-4-pyrimidinediamine. ^1H NMR (DMSO-d6): δ 8.09 (d, 1H), 8.00 (m, 1H), 7.42 (m, 2H), 7.05

(m, 1H), 4.53 (m, 2H), 4.25 (s, 2H), 3.15 (m, 2H); LCMS: ret. time: 20.35 min.; purity: 90 %; MS (m/e): 266 (MH^+).

7.1.21 2-Chloro-N4-(2-carboxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine (R940050)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2-carboxy-4-chloroaniline were reaeted to prepare 2-chloro-N4-(2-carboxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 20.83 min.; purity: 98%; ^1H NMR ($CDCl_3$): δ 8.64 (1H, d, J= 4.8 Hz), 8.24 (1H, d, J= 2.7 Hz), 7.76 (1H, dd, J= 8.7 and 2.7 Hz), 7.70 (1H, dd, J= 8.7 and J= 0.9 Hz).

7.1.22 N-(2-Chloro-5-fluoro-4-pyrimidinyl)-L-tyrosine Methyl Ester (R940108)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and L-tyrosine methyl ester were reacted to prepare N-(2-chloro-5-fluoro-4-pyrimidinyl)-L-tyrosine Methyl Ester. LCMS: ret. time: 23.32 min.; purity: 83%; MS (m/e): 325 (M+); ^1H NMR ($CDCl_3$): δ 7.90 (1H, d, J= 2.7 Hz), 6.95 (2H, d, J= 8.7 Hz), 6.75 (2H, d, J= 8.7 Hz), 5.95 (1H, s), 5.72 (1H, d, J= 7.5 Hz), 5.05 (1H, dt, J= 7.5 and 5.3 Hz), 3.77 (3H, s), 3.16 (2H, m).

7.1.23 2-Chloro-N4-[3-(5-cyano-2-methyl-4-thiomethyl-6-pyrimidinyl)phenyl]-5-fluoro-4-pyrimidineamine (R940141)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(5-eyano-2-methyl-4-thiomethyl-6-pyrimidinyl)aniline were reacted to prepare 2-chloro-N4-[3-(5-cyano-2-methyl-4-thiomethyl-6-pyrimidinyl)phenyl]-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 18.23 min.; purity: 84%; MS (m/e): 386 (M^+); ^1H NMR ($CDCl_3$): δ 8.19 (1H, t, J= 1.9 Hz), 8.11 (1H, d, J= 3.1 Hz), 7.98 (1H, dd, J= 8.1 and J= 2.4 Hz), 7.82 (1H, dd, J=7.8 and 1.8 Hz), 7.57 (1H, t, J= 7.8 Hz), 7.11 (1H, s), 2.79 (3H, s), 2.69 (3H, s).

7.1.24 N4-[4-(N-Benzylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R945154)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 4-(N-benzylpiperazino)aniline and 2,4-dichloro-5-

fluoropyrimidine gave N4-[4-(N-benzylpiperazino)phenyl]-2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 2.81 (m, 4 H), 3.37 (m, 6 H), 6.85 (br, 1 H), 6.93 (d, J= 9.0 Hz, 2 H), 7.40 (m, 5 H), 7.50 (d, J= 9.3 Hz, 2 H), 8.02 (d, J= 2.7 Hz, 1 H); LCMS: ret. time: 20.56 min, purity: 97.75%; MS (m/e): 398.00 (MH^+).

7.1.25 2-Chloro-N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine (R945069)

In a manner analogous to the preparation of N2,N4-bis(4-cyanomethyleneoxyphenyl)-5-fluoro-2,4-pyrimidinediamine, N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (178 mg, 0.6 mmol), trifluoroacetic anhydride (0.17 mL, 1.2 mmol) and pyridine (0.15 mL, 1.84 mmol) gave 2-chloro-N4-(4-cyanomethyleneoxyphenyl)-5-fluoro-4-pyrimidineamine (110 mg, 66%). ^{1}H NMR (acetone-d_6): δ 5.22 (s, 2 H), 7.24 (d, J= 9.3 Hz, 2 H), 7.62 (d, J= 9.0 Hz, 2 H), 8.94 (d, J= 1.8 Hz, 1 H); ^{19}F NMR (acetone-d_6): -137.60; LCMS: ret. time: 26.19 min.; purity: 89.93%; MS (m/e): 279.06 (MH^+).

7.1.26 N4-(4-Acetoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R940210)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-acetoxyaniline were reacted to prepare N4-(4-acetoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 25.97 min.; purity: 98%; MS (m/e): 281 (M^+); ^{1}H NMR ($CDCl_3$): δ 8.07 (1H, d, J= 2.7 Hz), 7.64 (2H, d, J= 9 Hz), 7.12 (2H, d, J= 9 Hz), 7.00 (1H, s), 2.31 (3H, s).

7.1.27 2-Chloro-5-fluoro-N4-(4-hydroxyphenyl)-4-pyrimidineamine (R940211)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-hydroxyaniline were reacted to prepare 2-chloro-5-fluoro-N4-(4-hydroxyphenyl)-4-pyrimidineamine. LCMS: ret. time: 20.10 min.; purity: 98%; MS (m/e): 240 (MH^+); ^{1}H NMR ($CDCl_3$): δ 8.02 (1H, d, J= 2.7 Hz), 7.46 (2H, d, J= 8.7 Hz), 6.86 (2H, d, J= 9 Hz), 6.85 (1H, s), 4.94 (1H, s).

7.1.28 2-Chloro-N4-(2,3-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine (R940213)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2,3-dimethyl-4-hydroxyaniline were reacted to prepare 2-chloro-N4-(2,3-dimethyl-4-hydroxyphenyl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 23.29 min.; purity: 93%; MS (m/e): 268 (MH^+); ^1H NMR ($CDCl_3$): δ 8.00 (1H, d, J= 2.7 Hz), 7.16 (1H, d, J= 8.7 Hz), 6.68 (1H, d, J= 8.7 Hz), 6.61 (1H, s), 4.87 (1H, s), 2.21 (3H, s), 2.16 (3H, s).

7.1.29 2-Chloro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine (R940230)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-hydroxy-5-methylaniline were reacted to prepare 2-chloro-N4-(3-chloro-4-hydroxy-5-methylphenyl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 26.26 min.; purity: 90%; ^1H NMR (DMSO-d6): δ 9.94 (1H, s), 9.21 (1H, s), 8.37 (1H, d, 3.6 Hz), 7.68 (1H, s), 7.41 (1H, s), 2.30 (3H, s).

7.1.30 2-Chloro-5-fluoro-N4-[4-[3-(N-morpholino)propyl]oxyphenyl]-4-pyrimidineamine (R940247)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-[3-(N-morpholino)propyl]oxyaniline were reacted to prepare 2-chloro-5-fluoro-N4-[4-[3-(N-morpholino)propyl]oxyphenyl]-4-pyrimidineamine. LCMS: ret. time: 17.15 min.; purity: 99%; MS (m/e): 367 (MH^+); ^1H NMR ($CDCl_3$): δ 8.02 (1H, d, J= 2.7 Hz), 7.49 (2H, d, J= 8.7 Hz), 6.92 (2H, d, J= 9 Hz), 6.85 (1H, s), 4.03 (2H, t, J= 6.3 Hz), 3.73 (4H, t, J= 4.6 Hz), 2.53 (2H, t, J= 6.7 Hz), 2.47 (4H, m), 1.98 (2H, m).

7.1.31 N4-[2-[4-(N-Benzylpiperazino)ethyl]]-2-chloro-5-fluoro-4-pyrimidineamine (R940259)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine 2,4-dichloro-5-fluoropyrimidine and 2-[4-(N-benzylpiperazino)ethylamine were reacted to prepare N4-[2-[4-(N-benzylpiperazino)ethyl]]-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 21.11 min.; purity: 96%; MS (m/e): 349 (M^+); ^1H NMR ($CDCl_3$): δ 7.88 (1H, d, J= 2.6 Hz), 7.31-7.17 (4H, m), 7.14 (1H, d, J=

1.7 Hz), 7.10 (1H, s), 3.76 (2H, m), 3.24 (2H, m), 2.90 (2H, m), 2.59 (2H, m), 2.34 (2H, m), 1.76 (4H, m).

7.1.32 N4-(3-*tert*-Butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R940268)

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-*tert*-butylaniline were reacted to prepare N4-(3-*tert*-butylphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 33.96 min.; purity: 98 %; MS (m/e): 279 (M^+); ^{1}H NMR ($CDCl_3$): δ 8.05 (1H, d, J= 3 Hz), 7.62 (1H, t, J= 1.3 Hz), 7.50 (1H, m), 7.34 (1H, t, J= 7.8 Hz), 7.22 (1H, m), 6.96 (1H, sl), 1.34 (9H, s).

7.1.33 2-Chloro-5-fluoro-N4-[3-(hydroxymethyl)phenyl]-4-pyrimidineamine (R925756)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobenzylalcohol were reacted to yield 2-chloro-5-fluoro-N4-[3-(hydroxymethyl)phenyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.45 (bs, 1H), 7.96 (d, 1H, J= 2.9 Hz), 7.65 (d, 1H, J= 8.2 Hz), 7.34 (s, 1H), 7.31 (t,1H, J= 8.2 Hz), 7.07 (d, 1H, J= 8.2), 4.52 (s, 2H)); ^{19}F NMR ($CDCl_3$): -44394 (s, 1F); LCMS: ret. time: 20.29 min.; purity: 100 %; MS (m/e): 254 (MH^+).

7.1.34 2-Chloro-5-fluoro-N4-[4-(hydroxymethyl)phenyl]-4-pyrimidineamine (R925759)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-aminobenzylalcohol were reacted to yield 2-chloro-5-fluoro-N4-[4-(hydroxymethyl)phenyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.08 (d, 1H, J= 2.7 Hz), 7.62 (d, 2H, J= 9.0 Hz), 7.40 (d, 2H, J= 8.1 Hz), 6.99 (bs, 1H), 4.70 (s, 2H); ^{19}F NMR ($CDCl_3$): -44570 (s, 1F); LCMS: ret. time: 19.57 min.; purity: 99%; MS (m/e): 254 (MH^+).

7.1.35 2-Chloro-N4-(3,3-dihydroisobenzofuranynl-1-one-6-yl)-5-fluoro-4-pyrimidineamine R940279

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-3,3-

dihydroisobenzofuran-1-one were reacted to give 2-chloro-N4-(3,3-dihydroisobenzofuranynl-1-one-6-yl)-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 21.15 min.; purity: 94.7 %; MS (m/e): 280 (MH^+).

7.1.36 2-Chloro-5-fluoro-N4-((2R)-hydroxy-(1S)-methyl-2-phenylethyl)-4-pyrimidineamine (R925762)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and (1R,2S)-(-)-norephedrine were reacted to yield 2-chloro-5-fluoro-N4-(2R-hydroxy-1S-methyl-2-phenylethyl)-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 7.85 (d, 1H, J= 3.0 Hz), 7.38 (m, 5H), 5.56 (d, 1H, J= 7.5 Hz), 5.00 (d, 1H, J= 3.0 Hz), 4.54 (m, 1H), 2.87 (bs, 1H), 1.10 (d, 1H, J= 6.9 Hz); ^{19}F NMR ($CDCl_3$): - 44408.

7.1.37 N-(2-Chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidinyl)glycine Ethyl Ester (R925850)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-6-ethoxycarbonyl-5-nitropyrimidine and glycine ethyl ester hydrochloride salt were reacted to yield N-(2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidinyl)glycine Ethyl Ester. ^1H NMR ($CDCl_3$): δ 8.87 (bs, 1H), 4.48 (q, 2H, J= 7.2 Hz), 4.39 (d, 2H, J= 5.1 Hz), 1.40 (t, 3H, J= 6.9 Hz), 1.33 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 28.27 min.; purity: 97%; MS (m/e): 332 (M^+).

7.1.38 2-Chloro-5-fluoro-N4-(2-hydroxy-2-phenylethyl)-4-pyrimidineamine (R925763)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2-amino-1-phenylethanol were reacted to yield 2-chloro-5-fluoro-N4-(2-hydroxy-2-phenylethyl)-4-pyrimidineamine. ^1H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 3.0 Hz), 7.41-7.32 (m, 5H), 5.71 (bs, 1H), 4.97 (d, 1H, J= 8.1 Hz), 3.98 (m, 1H), 3.56 (m, 1H), 2.57 (s, 1H); ^{19}F NMR ($CDCl_3$): - 45149; LCMS: ret. time: 22.27 min.; purity: 98%; MS (m/e): 263 (M^+).

7.1.39 2-Chloro-5-fluoro-N4-(furfuryl)-4-pyrimidineamine (R925764)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and

furfurylamine were reacted to yield 2-chloro-5-fluoro-N4-(furfuryl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.91 (d, 1H, J= 1.8 Hz), 7.39 (d, 1H, J= 1.2 Hz), 6.35 (m, 2H), 5.50 (bs, 1H), 4.69 (d, 2H, J= 5.1 Hz); ^{19}F NMR ($CDCl_3$): - 45163; LCMS: ret. time: 24.52 min.; purity: 97%; MS (m/e): 228 (M^+).

7.1.40 R935010: (±)-2-Chloro-5-fluoro-N4-[1-(4-hydroxyphenyl)ethyl]-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 1-(4-hydroxyphenyl)ethylamine to provide (±)-2-chloro-5-fluoro-N4-[1-(4-hydroxyphenyl)ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 2.3 Hz), 7.50-7.47 (dd, 2H, J= 1.7 and 8.7 Hz), 7.26-7.23 (dd, J= 8.7 and 1.7 Hz), 5.35-5.28 (m, 2H), 1.59 (d, 3H, J= 7.0 Hz).

7.1.41 R935011: (±)-N4-[1-(4-Bromophenyl)ethyl]-2-chloro-5-fluoro-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 1-(4-bromophenyl)ethylamine to provide (±)-N4-[1-(4-bromophenyl)ethyl]-2-chloro-5-fluoro- 4-pyrimidineamine: ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 2.3 Hz), 7.49 (d, 2H, J= 8.7 Hz), 7.25 (d, 2H, J= 8.7 Hz), 4.45-5.26 (m, 2H), 1.59 (d, 3H, J=7.0 Hz).

7.1.42 R935007: 2-chloro-5-fluoro-N4-[1-[(1*S*)-phenyl]ethyl]-4-pyrimidineamine

In like manner to the preparation of of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 1-(*1S*)-phenyl ethylamine were reacted to produce 2-chloro-5-fluoro-N4-[1-[(1*S*)-phenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.86 (d, 1H, J = 2.9 Hz), 7.37 (d, 4H, J = 4.7 Hz), 7.34-7.30 (m, 1H), 5.40-5.32 (m, 2H), 1.62 (d, 3H, J = 6.4 Hz); LCMS: ret. time: 29.5 min.; purity: 98%; MS (*m/e*): 252 (MH^+).

7.1.43 R935008: 2-Chloro-5-fluoro-N4-[1-[(1*R*)-pheny]lethyl]-4-pyrimidineamine

In like manner to the preparation of of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 1-(*1R*)-phenyl ethylamine

were reacted to produce 2-chloro-5-fluoro-N4-[1-[(*1R*)-phenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J = 2.9 Hz), 7.37 (d, 4H, J = 4.1 Hz), 7.34-7.30 (m, 1H), 5.38-5.31 (m, 2H), 1.62 (d, 3H, J = 6.4 Hz).

7.1.44 R935012: 2-Chloro-N4-[[di(3,5-di(trifluoromethyl)phenyl)]methyl]-5-fluoro-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with di[3,5-di(trifluoromethyl)phenyl]methylamine to provide 2-chloro-N4-[[di(3,5-di(trifluoromethyl)phenyl)]methyl]-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.06 (d, 1H, J= 2.3 Hz), 7.92 (s, 2H), 7.74 (s, 4H), 6.75 (d, 1H, J= 7.6 Hz), 5.80 (d, 1H, J= 7.0 Hz).

7.1.45 R935014: 2-Chloro-5-fluoro-N4-[1-[(1*R*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with (*R*)-(+)-1-(4-methoxyphenyl)ethylamine to provide 2-chloro-5-fluoro-N4-[1-[(1*R*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J= 2.3 Hz), 7.30 (d, 2H, J= 8.8 Hz), 6.89 (d, 2H, J= 8.8 Hz), 5.39-5.26 (m, 2H), 3.80 (s, 3H), 1.59 (d, 3H, J= 6.4 Hz).

7.1.46 R935015: 2-Chloro-5-fluoro-N4-[1-[(1*S*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3,4-ethylenedioxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with (*S*)-(-)-1-(4-methoxyphenyl)ethylamine to provide 2-chloro-5-fluoro-N4-[1-[(1*S*)-4-methoxyphenyl]ethyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J= 2.3 Hz), 7.31 (d, 2H, J= 8.8 Hz), 6.89 (d, 2H, J= 8.8 Hz), 5.38-5.29 (m, 2H), 3.80 (s, 3H), 1.59 (d, 3H, J= 7.7 Hz).

7.1.47 R935013: 2-Chloro-N-(fluoren-9-yl)-5-fluoro-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 9-aminofluorene hydrochloride and 2,4-dichloro-5-fluoropyrimidine

with added diisopropylethylamine were reacted to produce 2-chloro-N-(fluoren-9-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 1H, J= 2.3 Hz), 7.73 (d, 2H, J= 7.6 Hz), 7.59(d, 2H, J= 7.6 Hz), 7.44 (t, 2H, J= 7.6 Hz), 7.32 (app t, 2H, J= 7.6 Hz), 6.50 (d, 1H, J= 8.8 Hz), 5.45 (d, 1H, J= 8.4 Hz).

7.1.48 R935210: 2-Chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-6-yl]-4-pyrimidineamine

In like manner to the prepartation of 2-chloro-N-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, experiment, 2,4-dichloro-5-fluoropyrimidine was reacted with 4-(methoxycarbonylmethyleneoxy)aniline to produce 2-chloro-5-fluoro-N-[4-(methoxycarbonylmethyleneoxy)phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.17 (s, 1H), 8.33 (d, 1H, J= 3.5 Hz), 8.05 (s, 1H), 7.91 (s, 1H), 7.74 (d, 1H, J= 8.2 Hz), 7.40 (d, 1H, J= 7.6 Hz), 5.31 (s, 2H), 3.66 (s, 3H).

7.1.49 R935200: 2-Chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine:

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-1-methyl-indazoline were reacted to provide 2-chloro-5-fluoro-N-(1-methyl-indazoline-5-yl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.01 (s, 1H), 8.27 (d, 1H, J= 3.5 Hz), 8.04 (d, 1H, J= 1.7 Hz), 7.98 (d, 1H, J= 1.7 Hz), 7.64 (d, 1H, J= 8.8 Hz), 7.56 (dd, 1H, J= 1.7 and 8.8 Hz), 4.02 (s, 3H). LCMS: ret. time: 21.72 min.; purity: 99%; MS (*m/e*): 278 (MH^+).

7.1.50 R935017: N-(5-Bromo-2-chloropyrimidinyl)-4-fluorophenylethylamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 4-fluoro-α-methylbenzylamine and 5-bromo-2,4-dichloropyrimidine were reacted to produce N-(5-bromo-2-chloropyrimidinyl)-4-fluorophenylethylamine. ^{1}H NMR ($CDCl_3$): δ 8.12 (s, 1H), 7.35-7.25 (dd, 2H, J= 3.5 and 8.7 Hz), 7.05 (t, 1H, J= 8.7 Hz), 5.63 (d, 1H, J= 6.4 Hz), 5.36 (dq, 1H, 1H, J= 6.4 and 7.0 Hz), 1.60 (d, 3H, J= 7.0 Hz); LCMS: ret. time: 30.73 min.; purity: 94%; MS (*m/e*): 331 (MH^+).

7.1.51 R935009: (±)-N-(2-Chloro-5-fluoropyrimidinyl)-1-(4-fluorophenyl)ethylamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 4-fluoro-α-methylbenzylamine and 2,4-dichloro-5-fluoropyrimidine were reacted to produce (±)-N-(2-chloro-5-fluoropyrimidinyl)-1-(4-fluorophenyl)ethylamine. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 1H, J= 2.3 Hz), 7.37-7.33 (dd, 2H, J= 5.4 and 8.4 Hz), 7.04 (t, 2H, J= 8.4 Hz), 5.35-5.31 (m, 2H), 1.60 (d, 3H, J= 6.4 Hz); LCMS: ret. time: 32.90 min.; purity: 98%; MS (*m/e*): 270 (MH^+).

7.1.52 R935022: 5-Bromo-2-chloro-N4-[4-(N-methyl-2-methoxycarbonyl)ypyrrolyl)-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro 4-pyrimidineamine, 5-bromo-2,4-dichloropyrimidine and N-methyl-2-carbomethoxy-4-aminopyrrole hydrochloride with added diisopropylethylamine were reacted to produce the desired product 5-bromo-2-chloro-N-(N-methyl-2-carbomethoxypyrrol-4-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 7.43 (d, 1H, J= 1.8 Hz), 7.13 (br s, 1H), 6.84 (d, 1H, J= 1.8 Hz), 3.95 (s, 3H), 3.82 (s, 3H); LCMS: ret. time: 26.96 min.; purity: 91%; MS (*m/e*): 346 (MH^+).

7.1.53 R935234: 2-Chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-(4-aminophenoxymethyl)-3-phenyl-1,2-4-oxadiazole were reacted to produce 2-chloro-5-fluoro-N4-[4-(3-phenyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 9.92 (s, 1H), 8.26 (d, 1H, J= 3.5 Hz), 8.02-7.99 (m, 2H), 7.60-7.56 (m, 5H), 7.11 (d, 2H, J= 8.8 Hz), 5.58 (s, 2H); LCMS: ret. time: 32.09 min.; purity: 96%; MS (*m/e*): 398 (MH^+).

7.1.54 R935235: 2-Chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 5-(4-aminophenoxymethyl)-3-methyl-1,2-4-oxadiazole were reacted to produce 2-chloro-5-fluoro-N4-[4-(3-methyl-1,2,4-oxadiazol-5-yl)methyleneoxyphenyl]-4-pyrimidineamine. ^{1}H

NMR (DMSO-d_6): δ 9.91 (s, 1H), 8.26 (d, 1H, J= 3.5 Hz), 7.56 (d, 2H, J= 8.8 Hz), 7.05 (d, 2H, J= 8.8 Hz), 5.46 (s, 2H), 2.34 (s, 3H); LCMS: ret. time: 25.05 min.; purity: 98%; MS (*m/e*): 336 (MH^+).

7.1.55 R935236: 2-Chloro-5-fluoro-N4-[4-[(1-ethoxycarbonyl-1-methyl)ethyl]phenyl]-4-pyrimidineamine

In like manner to the preparation of 2-chloro-N4-(3,4-ethyleneioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-[1-ethoxycarbonyl-1-methyl)ethyl]aniline were reacted to produce 2-chloro-5-fluoro-N4-[4-[(1-ethoxyearbonyl-1-methyl)ethyl]phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 9.99 (s, 1H), 8.30 (d, 1H, J= 3.5 Hz), 7.60 (d, 2H, J= 8.8 Hz), 7.30 (d, 2H, J= 8.8 Hz), 4.04 (qt, 2H, J= 7.0 Hz), 1.47 (s, 6H), 1.10 (t, 3H, J= 7.0 Hz); LCMS: ret. time: 31.07 min.; purity: 97%; MS (*m/e*): 338 (MH^+).

7.1.56 2,4-Dichloro-5-ethoxycarbonylpyrimidine

A dry reaction flask equipped with a stirring bar and a reflux condenser was charged with 5-ethoxycarbonyluracil (1.84g, 10 mmol), $POCl_3$ (10 mL) and N,N-dimethylaniline (1 mL) and heated at 90 °C for 2h. The excess $POCl_3$ was removed under a reduced pressure and quenched with ice-water (100 g). The aqueous solution was extracted with ethyl ether (3 x 100 mL), washed with saturated aqueous $NaHCO_3$ solution and water (100 mL, each). After drying over sodium sulfate, the ethyl ether was removed and the residue was dried under a high vacuum to afford 2,4-dichloro-5-ethoxycarbonylpyrimidine.^{1}H NMR ($CDCl_3$): δ 9.00 (s, 1H), 4.45 (q, 2H, J= 6.9 Hz), 1.42 (t, 3H, J= 6.9 Hz).

7.1.57 N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester (R926518) and N-(4-Chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-phenylalanine Ethyl Ester (R926519)

A mixture of L-phenylalanine Ethyl Ester Hydrochloride (0.137g, 0.6 mmol) 2,4-dichloro5-ethoxycarbonylpyrimidine (0.112g, 0.5 mmol), triethylamine (0.7 mL, 0.6 mmol) in THF (4 mL) in a sealed tube was heated at 100 °C for 3h. The reaction was diluted with H_2O (20 ML), extracted with CH_2Cl_2 (3 x 50 mL), washed with 2N HCl (10 mL), water (10 mL) and solvent was evaporated. The residue obtained was purified by preparative TLC using 15% EtOAc in hexanes to obtain two products mainly, N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester (**R926518**). ^{1}H NMR ($CDCl_3$): δ 8.72 (d, 1H,

J= 6.92 Hz), 8.66 (s, 1H), 7.32-7.17 (m, 5H), 5.05 (dq, 1H, J= 1.2 and 5.7 Hz), 4.34 (q, 2H, J= 6.9 Hz), 4.20 (q, 2H, J= 5.1 Hz), 3.24 (dd, 1H, J= 5.4 Hz), 3.16 (dd, 1H, J= 7.5 Hz), 1.35 (t, 3H, J= 7.2 Hz), 1.24 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 37.15 min.; purity: 99%; MS (m/e): 378 (MH^+) and N-(4-chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-phenylalanine Ethyl Ester (**R926519**). ^1H NMR ($CDCl_3$): δ 8.83 (s, 1H), 7.28 (m, 3H), 7.18 (m, 2H), 6.00 (bt, 1H), 4.99 (bdq, 1H), 4.36 (q, 2H, J= 7.8 Hz), 4.19 (q, 2H, J= 6.9 Hz), 3.20 (t, 2H, J= 6.9 Hz). 1.38 (t, 3H, J= 4.5 Hz), 1.24 (t, 3H, J= 6 Hz); LCMS: ret. time: 34.80 min.; purity: 88%; MS (m/e): 378 (M^+).

7.1.58 N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-valine Ethyl Ester (R926520) and

N-(4-Chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-valine Ethyl Ester (R926521)

In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2,4-dichloro-5-ethoxycarbonylpyrimidine and L-valine Ethyl Ester were reacted to prepare N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-valine Ethyl Ester **(R926520).** ^1H NMR ($CDCl_3$): δ 8.80 (d, 1H, J= 8.1 Hz), 8.68 (s, 1H), 4.77 (dd, 1H, J= 4.8 Hz), 4.36 (q, 2H, J= 7.2 Hz), 4.24 (q, 2H, J= 6.6 Hz), 2.38 (m, 1H), 1.39 (t, 3H, J= 6.9 Hz), 1.29 (t, 3H, J= 7.2 Hz), 1.03 (d, 3H, J= 3 Hz), 1.00 (d, 3H, J= 2.7 Hz); LCMS: ret. time: 36.54 min.; purity: 89%; MS (m/e): 330 (MH^+) and N-(4-chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-valine Ethyl Ester **(R926521).** ^1H NMR ($CDCl_3$): δ 8.82 (s, 1H), 6.02 (m, 1H), 4.69 (dd, 1H, J= 4.8 and 4.5 Hz), 4.33 (q, 2H, J= 7.5 Hz), 4.23 (q, 2H, J= 7.5 Hz), 2.28 (sept, 1H). 1.34 (t, 3H, J= 6.9 Hz), 1.28 (t, 3H, J= 7 Hz), 1.00 (d, 6H, J= 7.2 Hz); LCMS: ret. time: 33.53 min.; purity: 91%; MS (m/e): 330 (M^+).

7.1.59 N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-leucine Ethyl Ester (R926522)

In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2,4-dichloro-5-ethoxycarbonylpyrimidine and L-leucine Ethyl Ester were reacted to prepare N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-leucine Ethyl Ester. ^1H NMR ($CDCl_3$): δ 8.69 (s, 1H), 8.64 (d, 1H, 7.8 Hz), 4.84 (s, 1H), 4.38 (q, 2H, J= 7.2 Hz), 3.75 (s, 3H), 1.73 (m, 2H), 1.39 (t, 3H, J= 6.9 Hz), 0.97 (d, 3H, J= 4.2 Hz), 0.95 (d, 3H, J= 4.8 Hz) ; LCMS: ret. time: 36.09 min.; purity: 92%; MS (m/e): 330 (MH^+).

7.1.60 N-(2-Chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-alanine Ethyl Ester (R926523) and

N-(4-Chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-alanine Ethyl Ester (R926524)

In like manner to the preparation of N-(2-chloro-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2,4-dichloro-5-ethoxycarbonylpyrimidine and L-valine Ethyl Ester were reacted to prepare N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-alanine Ethyl Ester **(R926523)**. ^{1}H NMR ($CDCl_3$): δ 8.80 (bd, 1H), 8.68 (s, 1H), 4.79 (q, 1H, J= 7.2 Hz), 4.35 (q, 2H, J= 7.2 Hz), 4.24 (m, 2H), 1.53 (d, 3H, J= 7.2 Hz), 1.38 (t, 3H, J= 7.2 Hz), 1.29 (t, 3H, J= 7.2 Hz); LCMS: ret. time: 31.89 min.; purity: 94%; MS (m/e): 303 (MH^+) and N-(4-chloro-5-ethoxycarbonyl-2-pyrimidinyl)-L-alanine Ethyl Ester **(R926524)**. ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 1H), 6.01 (bs, 1H), 4.65 (bq, 1H), 4.35 (q, 2H), 4.20 (q, 2H), 1.55, t, 3H), 1.40 (t, 3H), 1.25 (t, 3H); LCMS: ret. time: 28.78 min.; purity: 84%; MS (m/e): 302 (M^+).

7.1.61 2-Chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine

To a solution of 2,4-dichloro-5-fluoropyrimidine (0.5 g, 3.0 mmol) and 4-n-butoxyaniline (0.49 g, 3 mmol) in acetone/H_2O (1:9 mL) at room temperature was added concentrated HCl (0.1 mL). The mixture was heated at reflux for 1 h, cooled to room temperature, and made basic with 2 N NaOH (2 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude black solid was purified by chromatography (4:1 hexanes/EtOAc) to afford 2-chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine (0.71 g, 80%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 2.7 Hz, 1H), 7.51-7.46 (m, 2H), 6.95-6.89 (m, 2H), 6.83 (bs, 1H), 3.99-3.95 (t, J = 6.5 Hz, 2H), 1.82-1.57 (m, 2H), 1.53-1.43 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H).

7.1.62 2-Chloro-N4-(4-n-hexyloxyphenyl)-5-fluoro-4-pyridineamine

In like manner to the prepararion of 2-chloro-N4-(4-n-butyloxyphenyl)-5-fluoro-4-pyrimidineamine, the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-n-hexyloxyaniline gave 2-chloro-N4-(4-n-hexyloxyphenyl)-5-fluoro-4-pyridineamine. The crude product was purified by chromatography (4:1 $CHCl_3$/EtOAc) to afford (14) (0.74 g, 76%) as a red-brown oil that solidified upon standing: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 2.7 Hz, 1H),

7.50 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 6.84 (bs, 1H), 3.96 (t, J = 6.5 Hz, 2H), 1.83-1.74 (m, 2H), 1.48-1.41 (m, 2H), 1.36-1.34 (m, 4H), 0.93-0.89 (m, 3H).

7.1.63 N4-(3-Benzyloxyphenyl)-2-chloro-4-pyrimidineamine

A mixture of 2,6-dichloropyrimidine (2.00 g, 13.4 mmol), 3-benzyloxoaniline (2.07 g, 13.4 mmol) and triethylamine (2.72 g, 26.8 mmol) in 1-butanol (20 mL) was stirred at 50 °C for 17 h. The reaction mixture was concentrated to remove most of the 1-butanol, the crude product was preadsorbed onto silica gel using chloroform and purified by flash chromatography (95:5 chloroform/ methanol) to afford N4-(3-benzyloxyphenyl)-2-chloro-4-pyrimidineamine (1.70 g, 40%) as colorless oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.2 (s, 1H), 8.16 (d, J = 6.0 Hz, 1H), 7.48-7.24 (m, 7H), 7.12 (d, J = 9.0 Hz, 1H), 6.78 (m, 2H), 5.11 (s, 2H); ESI MS m/z 312 $[C_{17}H_{14}ClN_3O + H]^+$.

7.1.64 N4-[4-(tert-Butoxycarbonylmethyleneoxy)phenyl]-3-chloro-5-ethoxycarbonyl-4-pyrimidineamine (R926578)

In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 5-carboxyethoxy-2,4-dichloropyrimidine and tert-butyl 4-aminophenoxyacetatewere reacted to prepare N4-[4-(tert-butoxycarbonylmethyleneoxy)phenyl]-2-chloro-5-ethoxycarbonyl-2-chloro-4-pyrimidineamine. LCMS: MS (m/e): 407 (MH^+).

7.1.65 N4-(4-Ethoxyphenyl)-5-ethoxycarbonyl-2-trifluoromethyl-4-pyrimidineamine (R926059)

In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 4-chloro-5-ethoxycarbonyl-2-trifluoromethylpyrimidine and 4-ethoxyaniline were reacted to prepare N4-(4-ethoxyphenyl)-5-ethoxycarbonyl-2-trifluoromethyl-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 10.39 (s, 1H), 9.02 (s, 1H), 7.59 (dd, 2H, J= 2.1 and 7.2 Hz), 6.91 (dd, 2H, J= 1.8 and 6.6 Hz), 4.44 (q, 2H, J= 7.5 Hz), 4.06 (q, 2H, J= 7.2 Hz), 1.44 (m, 6H); LCMS: ret. time: 38.49 min.; purity: 100%; MS (m/e): 356 (MH^+).

7.1.66 N2-(4-Ethoxyphenyl)-5-methoxycarbonyl-4-trifluoromethyl-2-pyrimidineamine (R926060)

In like manner to the preparation of N-(2-chloro-5-ethoxycarbonyl-4-pyrimidinyl)-L-phenylalanine Ethyl Ester, 2-chloro-5-methoxycarbonyl-4-trifluoromethylpyrimidine and

4-ethoxyaniline were reacted to prepare N2-(2-ethoxyphenyl)-5-methoxycarbonyl-4-trifluoromethyl-2-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.98 (s, 1H), 7.47 (m, 3H), 6.91 (dd, 2H, J= 2.1 and 6.9 Hz), 4.05 (q, 2H, 6.9 Hz), 1.42 (t, 3H, J= 6.8 Hz); ^{19}F NMR ($CDCl_3$): -19105; LCMS: ret. time: 33.87 min; purity: 100%; MS (m/e): 342 (MH^+).

7.1.67 2-Chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853)

A reaction mixture containing 2,4-dichloro-5-fluoro-pyrimindine (1.2 equivalents) and 3-(tetrazol-5-yl)aniline (1 equivalents) in methanol:water (1:1; v/v) was heated at 60 °C for 24 h. Upon dilution with water and acidification, the solid formed was fitered, washed with water, dried and analyzed to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853). Alternatively this reaction can be achieved by treating 2,4-dichloro-5-fluoropyrimidine (1 equivalent) with 3-(tetrazol-5-yl)aniline (3 equivalents) in methanol:water (1:1; v/v) at 60 oC for 2-3 hours or at room temperature for 24 h to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.25 (s, 1H), 8.43 (s, 1H), 8.37 (d, 1H, J= 3.6 Hz), 7.90 (dd, 1H, J= 0.9 and 9 Hz), 7.75 (d, 1H, J= 7.5 Hz), 7.61 (t, 1H, J= 7.8 Hz); LCMS: purity: 90%; MS (m/e): 292 (MH^+).

7.1.68 2-Chloro-N4-(2,5-dimethoxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine (R926858)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 2,5-dimethoxy-4-chloroaniline gave 2-chloro-N4-(2,5-dimethoxy-4-chlorophenyl)-5-fluoro-4-pyrimidineamine. LCMS: purity: 97%; MS (m/e): 316 (M-2H) and 320 (M+2H).

7.1.69 2-Chloro-5-fluoro-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-4-pyrimidineamine (R926861)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-methoxycarbonyl-5-trifluoromethylaniline gave 2-chloro-5-fluoro-N4-(3-methoxycarbonyl-5-trifluoromethylphenyl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.60 (s, 1H), 8.43 (s, 1H), 8.20 (d, 1H, J= 3 Hz), 7.99 (s, 1H), 3.96 (s, 3H); ^{19}F NMR (CD_3OD): -18332, - 18374; and - 44259; LCMS: purity: 91%; MS (m/e): 350 (MH^+).

7.1.70 2-Chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl)-4-pyrimidineamine (R926869)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-(2-phenyl-1,3,4-oxadiazol-5-yl)aniline gave 2-chloro-5-fluoro-N4-[3-(2-phenyl-1,3,4-oxadiazol-5-yl)phenyl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.28 (s, 1H), 8.62 (s, 1H), 8.39 (d, 1H, J= 3.3 Hz), 8.11 (m, 2H), 7.98 (bd, 1H, J= 6.9 Hz), 7.88 (bd, 1H, J= 8.4 Hz), 7.65 (m, 4H); LCMS: purity: 76%; MS (m/e): 76%.

7.1.71 2-Chloro-N4-[3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl)-5-fluoro-4-pyrimidineamine (R926873)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)aniline gave 2-chloro-N4-[3-(2-ethoxycarbonylmethylene-1,3,4-oxadiazol-5-yl)phenyl]-5-fluoro-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.42 (t, 1H, J= 1.8 Hz), 8.19 (d, 1H, J= 3.3 Hz), 7.99 (dt, 1H, J= 1.2 and 8.1 Hz), 7.82 (dt, 1H, J= 1.2 and 8.1 Hz), 7.58 (t, 1H, J= 9 Hz), 4.24 (q, 2H, J= 3.9 Hz), 4.17 (s, 2H), 1.28 (t, 3H, J= 7.2 Hz); LCMS: purity: 85%; MS (m/e): 379 (MH^+).

7.1.72 2-Chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine (R926875)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-trifluoromethoxyaniline gave 2-chloro-5-fluoro-N4-(4-trifluoromethoxyphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.11 (d, 1H, J= 2.1 Hz), 7.68 (dd, 2H, J= 2.4 and 7.6 Hz), 7.26 (dd, 2H, J= 3 and 8.7 Hz), 7.0 (bs, 1H); ^{19}F NMR (CD_3OD): δ –16517 and –44523; LCMS: purity: 94%; MS (m/e): 308 (MH^+).

7.1.73 2-Chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine (R926876)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-trifluoromethylaniline gave 2-chloro-5-fluoro-N4-(4-trifluoromethylphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 2.1 Hz), 7.80 (d, 2H, J= 7.1 Hz), 7.66 (d,

2H, J= 9 Hz), 7.10 (bs, 1H); ^{19}F NMR ($CDCl_3$): -17682 and - 44362; LCMS: purity: 91% and MS (m/z): 292 (MH^+).

7.1.74 2-Chloro-N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-4-pyrimidineamine (R926877)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-chloro-3-trifluoromethylaniline gave 2-chloro-N4-(4-chloro-3-trifluoromethylphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J= 2.1 Hz), 7.96 (d, 1H, J= 3 Hz), 7.91 (dd, 1H, J= 2.7 Hz and 8.7 Hz), 7.53 (d, 1H, J= 8.1 Hz), 7.06 (bs, 1H); ^{19}F NMR ($CDCl_3$): - 17892 and - 44402; LCMS: purity: 93%; MS (m/e): 326 (M^+).

7.1.75 2-Chloro-5-fluoro-N4-(6-methoxypyridin-3-yl)-4-pyrimidineamine (R926878)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-amino-6-methoxypyridine gave 2-chloro-5-fluoro-N4-(6-methoxypyridin-3-yl)-4-pyrimidineamine. ^{1}H NMR (CD_3OD): δ 8.39 (d, 1H, J= 3.0 Hz), 8.10 (d, 1H, J= 3.6 Hz), 7.95 (dd, 1H, J= 2.4 and 9 Hz), 8.30 (d, 1H, J= 9 Hz), 3.91 (s, 3H); ^{19}F NMR (CD_3OD): - 44737; LCMS: purity: 97%; MS (m/e): 255 (M^+).

7.1.76 2-Chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine (R926882)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,4-difluoroaniline gave 2-chloro-N4-(3,4-difluorophenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H, J= 2.1 Hz), 7.72 (m, 1H), 7.22 (m, 2H), 6.95 (bs, 1H); LCMS: purity: 93%; MS (m/e): 260 (M^+).

7.1.77 2-Chloro-N4-(3,4-Dichlorophenyl)-5-fluoro-4-pyrimidineamine (R926884)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,4-dichloroaniline gave 2-chloro-N4-(3,4-dichlorophenyl)-5-fluoro-4-pyrimidineamine. LCMS: purity: 95%; MS (m/e): 294 (M+ 2H).

7.1.78 2-Chloro-5-fluoro-N4-(6-methylpyridin-2-yl)-4-pyrimidineamine (R926888)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 2-amino-6-methylpyridine gave 2-chloro-5-fluoro-N4-(6-methylpyridin-2-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.23 (s, 1H), 8.19 (s, 1H), 8.12 (d, 1H, J= 3 Hz), 7.55 (bs, 1H), 7.69 (t, 1H, J= 7.4 Hz), 9.35 (d, 1H, J= 7.5 Hz); 19F NMR (CDCl3): - 44073; LCMS: purity: 96%; MS (m/e): 239 (M^+).

7.1.79 2-Chloro-N4-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine (R926889)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-amino-2.6-dimethoxypyridine gave 2-chloro-N4-(2,6-dimethoxypyridin-3-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.57 (d, 1H, J= 8.7 Hz), 8.02 (d, 1H, J= 2.7 Hz), 6. 40 (d, 1H, J= 8.1 Hz), 4.03 (s, 3H), 3.98 (s, 3H); ^{19}F NMR ($CDCl_3$): - 44640; LCMS: purity: 90%; MS (m/e): 285 (M^+).

7.1.80 2-Chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine (R920400)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-amino-6-chloropyridine gave 2-chloro-N4-(6-chloropyridin-3-yl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.53 (d, 1H, J= 3 Hz), 8.25 (dd, 1H, J= 3 and 9 Hz), 8.15 (d, 1H, J= 2.4 Hz), 7.39 (d, 1H, J= 8.7 Hz), 7.00 (bs, 1H); LCMS: purity: 98%; MS (m/e): 259 (M^+).

7.1.81 2-Chloro-5-fluoro-N4-(4-methylpyridin-2-yl)-4-pyrimidineamine (R920401)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 2-amino-4-methylpyridine gave 2-chloro-5-fluoro-N4-(4-methylpyridin-2-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.22 (s, 1H), 8.16 (d, 1H, J= 8.4 Hz), 8.13 (d, 1H, J= 2.4 Hz), 6.91 (d, 1H, J= 5.4 Hz), 2.42 (s, 3H); LCMS: purity: 87%; MS (m/e): 239 (MH^+).

7.1.82 2-Chloro-5-fluoro-N4-(3-trifluoromethoxyphenyl)-4-pyrimidineamine (R920402)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-trifluoromethoxyaniline gave 2-chloro-5-fluoro-N4-(3-trifluoromethoxyphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.12 (d, 1H, J= 3 Hz), 7.68 (bs, 1H), 7.53 (dd, 1H, J= 1.2 and 8.4 Hz), 7.41 9t, 1H, J= 8.1 Hz), 7.04 (bdt, 2H); ^{19}F NMR ($CDCl_3$): -16430 and -44463; LCMS: purity: 89%; MS (m/e): 308 (MH^+).

7.1.83 2-Chloro-N4-(3,4-Difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine (R920403)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3,4-difluoromethylenedioxyaniline gave 2-chloro-N4-(3,4-difluoromethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.09 (d, 1H, J= 3 Hz), 7.70 (d, 1H, J= 2.4 Hz), 7.10 (dd, 1H, J= 2.4 and 8.7 Hz), 7.06 (t, 1H, J= 8.1 Hz), 6.97 (bs, 1H); ^{19}F NMR ($CDCl_3$): - 14175 and - 44562; LCMS: purity: 95%; MS (m/e): 304 (MH^+).

7.1.84 2-Chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine (R920409)

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 6-aminoquinoline gave 2-chloro-5-fluoro-N4-(quinolin-6-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.02 (dd, 1H, J= 2.7 Hz), 8.00 (dd, 1H, J= 2.4 Hz), 7.73 (d, 1H, J= 9 Hz), 7.68 (dd, 1H, J= 2.4 and 8.7 Hz), 7.28 (t, 1H, J= 10.5 Hz), 6.42 (d, 1H, J= 9.3 Hz); ^{19}F NMR ($CDCl_3$): - 44344; LCMS: purity: 91%; MS (m/e): 292 (M^+).

7.1.85 2-Chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 3-chloro-4-trifluoromethoxyaniline gave 2-chloro-N4-(3-chloro-4-trifluoromethoxyphenyl)-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, 1H, J= 3.0 Hz), 7.86 (d, 1H, J= 2.1 Hz), 7.61 (dd, 1H, J= 2.1 and 8.7 Hz), 7.35 (dd, 1H, J= 1.2 and 8.7 Hz), 6.98 (bs, 1H); LCMS: purity: 97%; MS (m/e): 342 (M+2H).

7.1.86 2-Chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-pyrimidineamine

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 4-chloro-3-methoxyaniline gave 2-chloro-N4-(4-chloro-3-methoxyphenyl)-5-fluoro-4-aminopyrimidine. LCMS: purity: 88%; MS (m/e): 288 (MH^+).

7.1.87 2-Chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidinediamine

In like manner to the preparation of 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine the reaction of 2,4-dichloro-5-fluoropyrimidine with 5-amino-2-(2-hydroxyethyloxy)pyridine gave 2-chloro-5-fluoro-N4-[2-(2-hydroxyethyleneoxy)pyridin-5-yl]-4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.28 (d, 1H, J= 2.4 Hz), 8.08 (m, 1H), 7.99 (m, 1H), 7.00 (bs, 1H), 6.87 (bd, 1H), 4.47 (m, 2H), 3.97 (m, 2H).

7.1.88 2-Chloro-N4-[2-(2-chloro-5-fluoropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-5-fluoro-4-pyrimidineamine (R926910)

In a like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1,2,3,4-tetrahydroisoquinoline were reacted to provide 2-chloro-N4-[2-(2-chloro-5-fluoropyrimidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-5-fluoro-4-pyrimidineamine.^1H NMR ($CDCl_3$): δ 8.08 (d, 1H, J= 3.0 Hz), 7.95 (d, 1H, J= 6.0 Hz), 7.50-7.42 (m, 2H), 7.21 (d, 1H, J= 8.4 Hz), 6.96-6.90 (m, 1H), 4.95 (s, 2H), 4.04 (t, 2H, J= 5.7 Hz), 2.99 (t, 2H, J= 5.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -42555, -44573; LCMS: purity: 98%; MS (m/e): 410(MH^+).

7.1.89 2-Chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine (R926911)

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline were reacted to provide 2-chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine.

^{1}H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.50-7.26 (m, 2H), 7.19-7.11 (m, 2H), 4.57 (s, 2H), 3.64 (t, 2H, J= 5.7 Hz), 2.80 (t, 2H, J= 5.7 Hz), 1.48 (s, 9H); LCMS: purity: 89%; MS (m/e): 379(M^+).

7.1.90 2-Chloro-5-fluoro-N4-(1,2,3,4-tetrahydroisoquinolin-7-yl)-4-pyrimidineamine (R926912)

A solution of 2-chloro-5-fluoro-N4-[2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]-4-pyrimidineamine in 40% trifluoroacetic acid/dichloromethane was stirred at rt for 30 min. Removal of the solvent left an oily residue which was suspended in water, made basic with $NaHCO_3$, and extracted with ethyl acetate. Purification by column chromatography over silica gel provided 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydroisoquinolin-7-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 1H, J= 3.0 Hz), 7.37 (dd, 1H, J= 2.4 and 8.4 Hz), 7.27 (d, 1H, J= 1.5 Hz), 7.11 (d, 1H, J= 8.4 Hz), 6.92 (s, 1H), 4.04 (s, 2H), 3.15 (t, 2H, J= 6.0 Hz), 2.79 (t, 2H, J= 6.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -44648; LCMS: purity: 97%; MS (m/e): 279(MH^+).

7.1.91 2-Chloro-5-fluoro-N4-(4-methyl-3-trifluoromethylphenyl)-4-pyrimidineamine (R926920)

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-methyl-3-trifluoromethylaniline were reacted to provide 2-chloro-5-fluoro-N4-(4-methyl-3-trifluoromethylphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 1H, J= 3.0 Hz), 7.85-7.78 (m, 2H), 7.33 (d, 1H, J= 9.3 Hz), 6.96 (bs, 1H), 2.48 (d, 3H, J= 1.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -17641, -44541; LCMS: purity: 97%; MS (m/e): 306(MH^+).

7.1.92 2-Chloro-5-fluoro-N4-(4-fluoro-3-methylphenyl)-4-pyrimidineamine (R926921)

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-fluoro-3-methylaniline were reacted to provide 2-chloro-5-fluoro-N4-(4-fluoro-3-methylphenyl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.06 (d, 1H, J= 2.4 Hz), 7.48-7.43 (m, 1H), 7.39 (dd, 1H, J= 2.7 and 6.3 Hz), 7.03 (t, 1H, J= 9.0 Hz), 6.84 (bs, 1H), 2.30 (d, 1H, J= 1.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): -34285, -44676; LCMS: purity: 95%; MS (m/e): 257(MH^+).

7.1.93 N4-[3-[(N-t-butoxycarbonyl)aminomethyl]-4-methylphenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R926924)

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-[(N-t-butoxycarbonyl)aminomethyl]-4-methylaniline were reacted to provide N4-[3-[(N-t-butoxycarbonyl)aminomethyl]-4-methylphenyl]-2-chloro-5-fluoro-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 1H, J= 3.0 Hz), 7.52 (d, 1H, J= 9.3 Hz), 7.45 (s, 1H), 7.19 (d, 1H, J= 8.1 Hz), 6.96-6.89 (m, 1H), 4.80 (bs, 1H), 2.31 (s, 2H), 1.46 (s, 9H); LCMS: purity: 97%; MS (m/e): 311 (M – (*t*-butyl) $^+$).

7.1.94 2-Chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino] methyl]phenyl]-5-fluoro-4-pyrimidineamine

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 1-(3-aminobenzyl)piperidine-4-carboxylate were reacted to provide 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]methyl]phenyl]-5-fluoro-4-pyrimidineamine. LCMS: purity: 97%; MS (m/e): 394(MH^+).

7.1.95 2-Chloro-N4-[3-[4-(ethoxycarbonyl)piperidino carbonyl]phenyl]-5-fluoro-4-pyrimidineamine

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-[[4-(ethoxycarbonyl)piperidino]carbonyl]aniline were reacted to provide 2-chloro-N4-[3-[[4-(ethoxycarbonyl)piperidino]carbonyl]phenyl]-5-fluoro-4-pyrimidineamine. LCMS: purity: 96%; MS (m/e): 407(M^+).

7.1.96 2-Chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine

In a manner similar to the preparation of N4-(3,4-ethylenedioxy)-5-fluoro-N2-[2-(hydroxymethyl)benzofuran-5-yl]-2,4-pyrimidinediamine, 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-4-pyrimidineamine was reduced with Dibal-H to yield 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-hydroxynaphthalen-7-yl)-4-pyrimidineamine.

^{1}H NMR ($CDCl_3$): δ 8.05 (d, 1H, J= 3.0 Hz), 7.59 (d, 1H, J= 2.4 Hz), 7.14 (d, 1H, J= 8.1 Hz), 6.93 (bs, 1H), 4.82-4.78 (m, 1H), 2.82-2.71 (m, 2H), 2.08-1.74 (m, 5H) ; ^{19}F NMR (282 MHz, $CDCl_3$): -44661; LCMS: purity: 94%; MS (m/e): 294(MH^+).

7.1.97 2-Chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-4-pyrimidineamine.

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1-tetralone were reacted to provide 2-chloro-5-fluoro-N4-(1,2,3,4-tetrahydro-1-oxonaphthalen-7-yl)-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.31 (d, 1H, J= 3.3 Hz), 8.15 (d, 1H, J= 2.4 Hz), 7.82 (dd, 1H, J= 2.4 and 8.1 Hz), 7.36 (d, 1H, J= 8.1 Hz), 2.91 (t, 2H, J= 6.0 Hz), 2.59 (t, 2H, J= 6.0 Hz), 2.07-1.98 (m, 2H); LCMS: purity: 93%; MS (m/e): 294(MH^+).

7.1.98 2-Chloro-5-fluoro-N4-[3-(trifluoromethylthio)phenyl]-4-pyrimidineamine

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(trifluoromethylthio)aniline were reacted to provide 2-chloro-5-fluoro-N4-[3-(trifluoromethylthio)phenyl]-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 8.13 (bs, 1H), 7.92 (bs, 1H), 7.89-7.84 (m, 1H), 7.48-7.45 (m, 2H), 7.04 (bs, 1H); LCMS: purity: 97%; MS (m/e): 325(MH^+).

7.1.99 2-Chloro-5-fluoro-N4-[(3-dihydroxyboryl)phenyl)]-4-pyrimidineamine

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-aminobenzeneboronic acid were reacted to provide 2-chloro-5-fluoro-N4-[(3-dihydroxyboryl)phenyl)]-4-pyrimidineamine.

7.1.100 2-Chloro-5-fluoro-N4-[(1H)-indol-6-yl]-4-pyrimidineamine

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-aminoindole were reacted to provide 2-chloro-5-fluoro-N4-[(1H)- indol-6-yl]-4-pyrimidineamine. LCMS: purity: 92%; MS (m/e): 263(MH^+).

7.1.101 2-Chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methylaniline were reacted to provide 2-chloro-5-fluoro-N4-(2-hydroxy-4-methylphenyl)-4-pyrimidineamine. LCMS: purity: 97%; MS (m/e): 255(MH^+).

7.1.102 2-Chloro-5-fluoro-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-4-pyrimidineamine

In a like manner to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2-(methoxycarbonyl)-(1H)-indole were reacted to provide 2-chloro-5-fluoro-N4-[2-(methoxycarbonyl)-(1H)-indol-6-yl]-4-pyrimidineamine which was used without further purification. LCMS: purity: 65%; MS (m/e): 322(MH^+).

7.1.103 N4-[3-(4-(2-Chloro-5-fluoropyrimidine)-N-aminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R940298)

The reaction flask equipped with a magnetic stirring bar and a rubber septum (to prevent loss of 2,4-dichloro-5-fluoropyrimidine and N_2 inlet was charged 3-aminobenzylamine (0.22 g, 1.79 mmol), MeOH (1 mL), H_2O (3 mL) and 2,4-dichloro-5-fluoropyrimidine (0.3 g, 1.79 mmol). The reaction mixture was stirred at 80°C for 30 min., cool to room temperature, diluted with H_2O (30 mL). Upon saturation with sodium chloride it was extracted with ethyl acetate (3 x 20 mL), dried over anhydrous sodium sulfate and the solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh) using 1 to 3% MeOH in CH_2Cl_2 to obtain N4-[3-(4-(2-chloro-5-fluoropyrimidine)-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine **R940298.** ^{1}H NMR (DMSO-d6): δ 10.09 (1H, s), 8.88 (1H, t, *J*= 5.85 Hz), 8.40 (1H, d, *J*= 3.6 Hz), 8.23 (1H, d, *J*= 3.3 Hz), 7.74 (1H, s), 7.70 (1H, d, *J*= 8.1 Hz), 7.44 (1H, t, *J*= 7.8 Hz), 7.19 (1H, d, *J*= 8.1 Hz), 4.69 (2H, d, *J*= 5.7 Hz ; purity 92 %.

7.1.104 2-Chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine (R940302)

The reaction flask equipped with a magnetic stirring bar and a rubber septum (to prevent loss of 2,4-dichloro-5-fluoropyrimidine and N_2 inlet was charged with 3-methyloxycarbonyl-4-methoxyaniline (0.88 g, 4.86 mmol), MeOH (3 mL), H_2O (7 mL) and

2,4-dichloro-5-fluoropyrimidine (0.81 g, 4.86 mmol). The reaction mixture was stirred at 60°C for 30 min., diluted with H_2O (50 mL), acidified with 2N HCl (6 mL) and sonicated. The solid obtained was filtered, washed with H_2O and dried to produce 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine **R940302.** ^{1}H NMR (DMSO-d6): δ 10.10 (1H, s), 8.39 (1H, d, *J*= 3.6 Hz), 8.04 (1H, d, *J*= 2.7 Hz), 7.98-7.93 (1H, m), 7.30 (1H, d, *J*= 9 Hz), 3.92 (3H, s), 3.89 (3H, m) ; purity 96% ; MS (m/e): 312 (MH+).

7.1.105 2-Chloro-5-fluoro-N4-(4-phahthlimide)-4-pyrimidineamine (R940303)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 4-aminophthalimide were reacted to produce 2-chloro-5-fluoro-N4-(4-phahthlimide)-4-pyrimidineamine **R940303.** ^{1}H NMR (DMSO-d6): δ 11.38 (1H, s), 10.60 (1H, s), 8.57 (1H, d, *J*= 3.3 Hz), 8.39 (1H, d, *J*= 1.8 Hz), 8.18 (1H, dd, *J*= 8.4 Hz, *J*= 2.1 Hz), 7.93 (1H, d, *J*= 8.1 Hz) ; purity 90% ; MS (m/e): 293 (MH+).

7.1.106 2-Chloro-5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-4-pyrimidineamine (R940305)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-methylaminocarbonyl-4-methoxyaniline were reacted to produce 2-chloro-5-fluoro-N4-(3-methylaminocarbonyl-4-methoxyphenyl)-4-pyrimidineamine **R940305.** ^{1}H NMR (DMSO-d6): δ 9.91 (1H, s), 8.31 (1H, d, *J*= 3.6 Hz), 8.11 (1H, d, *J*= 2.7 Hz), 7.78 (1H, dd, *J*= 9 Hz, *J*= 2.7 Hz), 7.59 (1H, m), 6.87 (1H, d, *J*= 9 Hz), 3.90 (3H, s), 2.96 (3H, d, *J*= 4.5 Hz) ; purity 93%.

7.1.107 N2-Chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine (R940313)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(N-morpholinomethylene)-4-methoxyaniline were reacted to produee 2-chloro-5-fluoro-N4-[3-(N-morpholinomethylene)-4-methoxyphenyl]-4-pyrimidineamine **R940313.**^{1}H NMR (DMSO-d6): δ 10.00 (1H, s), 8.35 (1H, d, *J*= 3.3 Hz), 7.72 (1H, d, *J*= 3 Hz), 7.58 (1H, d,

J= 9.3 Hz), 7.12 (1H, d, *J*= 8.4 Hz), 3.89 (3H, s), 3.8-3.5 (6H, m), 2.58 (4H, m) ; purity 96% ; MS (m/e): 352 (M).

7.1.108 N4-[3-(N-*tert*-Butoxycarbonyl-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine (R940315)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(N-*tert*-butoxycarbonyl-N-methylaminomethylene)-aniline were reacted to produce N4-[3-(N-*tert*-butoxycarbonyl-N-methylaminomethylene)-phenyl]-2-chloro-5-fluoro-4-pyrimidineamine **R940315.** ^{1}H NMR (DMSO-d6): δ 10.13 (1H, s), 8.42 (1H, d, *J*= 3.6 Hz), 7.69 (1H, m), 7.64 (1H, s), 7.45 (1H, t, *J*= 7.6 Hz), 7.09 (1H, d, *J*= 7.8 Hz), 4.48 (2H, s), 2.90 (3H, s), 1.49 (9H, m) ; purity 92% ; MS (m/e): 367 (MH+).

7.1.109 N4-(3-(N-*tert*-Butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)- 2-chloro-5-fluoro-4-pyrimidineamine (R940320)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxy-aniline were reacted to produce N4-(3-(N-*tert*-butoxycarbonyl-N-*iso*-propylaminomethylene)-4-methoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine **R940320.** ^{1}H NMR (DMSO-d6): δ 10.01 (1H, s), 8.34 (1H, d, *J*= 3.6 Hz), 7.52 (2H, m), 7.08 (1H, d, *J*= 8.7 Hz), 4.33 (3H, m), 3.90 (3H, s), 1.50-1.30 (9H, m), 1.18 (6H, d, *J*= 6.9 Hz) ; purity 95%.

7.1.110 2-Chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine (R940322)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one were reacted to produce 2-chloro-N4-[(2,2-dimethyl-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine **R940322.** ^{1}H NMR (DMSO-d6): δ 10.89 (1H, s), 10.04 (1H, s), 8.38 (1H, d, *J*= 3.6 Hz), 7.35 (2H, m), 7.04 (1H, d, *J*= 8.4 Hz), 1.50 (6H, s) ; purity 91.4% ; MS (m/e): 322 (M).

7.1.111 2-Chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-(pyridyl-1-oxide)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine (R940328)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 2-(6-amino-3-dihydro-2,2-dimethyl-benzo[1,4]oxazin-4-yl)pyridine 1-Oxide were reacted to produce 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-(pyridyl-1-oxide)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine **R940328.** ^{1}H NMR (DMSO-d6): δ 9.82 (1H, s), 8.39 (1H, dd, *J*= 6.3 Hz, *J*= 1.2 Hz), 8.30 (1H, d, *J*= 3.6 Hz), 7.63 (1H, dd, *J*= 8.4 Hz, *J*= 2.4 Hz), 7.47 (1H, td, *J*= 7.5 Hz, *J*= 1.8 Hz), 7.34 (1H, m), 7.21 (1H, dd, *J*= 8.7 Hz, *J*= 2.4 Hz), 7.07 (1H, d, *J*= 2.7 Hz), 6.91 (1H, d, *J*= 8.7 Hz), 3.64 (2H, s), 1.41 (6H, s) ; purity 95.8% ; MS (m/e): 402 (MH+).

7.1.112 2-Chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine (R940336)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazine were reacted to produce 2-chloro-N4-[3-dihydro-2,2-dimethyl-4-(2-pyridyl)-benzo[1,4]oxazin-6-yl]-5-fluoro-4-pyrimidineamine **R940336.** ^{1}H NMR (DMSO-d6): δ 9.95 (1H, s), 8.38 (1H, dd, *J*= 4.8 Hz, *J*= 1.8 Hz), 8.33 (1H, d, *J*= 3.6 Hz), 7.84 (1H, d, *J*= 2.1 Hz), 7.79 (1H, ddd, *J*= 15.6 Hz, *J*= 7.2 Hz, *J*= 2.1 Hz), 7.57 (1H, d, *J*= 8.4 Hz), 7.19 (1H, dd, *J*= 8.4 Hz, *J*= 2.4 Hz), 7.01-6.95 (2H, m), 3.96 (2H, s), 1.32 (6H, s) ; purity 99.3% ; MS (m/e): 386 (MH+).

7.1.113 2-Chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine (R940342)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2,2-difluoro-4H-benzo[1,4]oxazin-3-one were reacted to produce 2-chloro-N4-[(2,2-difluoro-4H-benzo[1,4]oxazin-3-one)-6-yl]-5-fluoro-4-pyrimidineamine **R940342.** ^{1}H NMR (DMSO-d6): δ 12.24 (1H, s), 10.23 (1H, s), 8.45 (1H, dd, *J*= 3.3 Hz, *J*= 0.9 Hz), 7.66 (1H, dd, *J*= 4.2 Hz, *J*= 2.4 Hz), 7.55 (1H, dt, *J*= 9 Hz, *J*= 2.5 Hz), 7.43 (1H, d, *J*= 9 Hz+); ^{19}F NMR (DMSO-d6): δ -21582, -43415 ; purity 96.2%; MS (m/e) : 331 (MH+).

7.1.114 2-Chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-4-pyrimidineamine (R940344)

In like manner to the preparation of 2-chloro-5-fluoro-N4-(3-methyloxycarbonyl-4-methoxyphenyl)-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one were reacted to produce 2-chloro-N4-[(2,2-dimethyl-4H-5-pyrido[1,4]oxazin-3-one)-7-yl]-5-fluoro-4-pyrimidineamine **R940344.** ^{1}H NMR (DMSO-d6): δ 11.32 (1H, s), 10.20 (1H, s), 8.45 (1H, d, *J*= 3.6 Hz), 8.33 (1H, d, *J*= 2.1 Hz), 7.84 (1H, d, *J*= 2.1 Hz), 1.54 (6H, s) ; purity 90.8% ; MS (m/e): 324 (MH+).

7.1.115 N4-(4-Aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine (R945028)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine (250 mg, 1.50 mmol) and 4-aminocarbonylmethyleneoxyaniline (540 mg, 3.25 mmol) were reacted to yield N4-(4-aminocarbonylmethyleneoxyphenyl)-2-chloro-5-fluoro-4-pyrimidineamine. LCMS: ret. time: 18.34 min.; purity: 100%; MS (m/e): 298.47 (MH^+).

7.1.116 2-Chloro-5-fluoro-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-4-pyrimidineamine (R945298)

In a manner similar to the preparation of 2-chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one were reacted to yield 2-chloro-5-fluoro-N4-[2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one-6-yl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 4.63 (s, 2H), 7.34 (d, J= 8.7 Hz, 1H), 7.44 (d, J= 8.4 Hz, 1H), 8.33 (d, J= 3.3 Hz, 1H), 10.14 (s, 1H, NH), 11.19 (s, 1H, NH); ^{19}F NMR (282 MHz, DMSO-d_6): δ - 152.35; LCMS: ret. time: 26.74 min.; purity: 85.90%; MS (m/e): 296.13 (MH^+).

7.1.117 N4-(1,4-Benzoxazin-6-yl)-N2-chloro-5-fluoropyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-1,4-benzoxazine were reacted to yield N4-(1,4-Benzoxazin-6-yl)-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) purity 95 % MS (m/e): 281(MH^+).

7.1.118 N4-(1,4-Benzoxazin-7-yl)]-N2-chloro-5-fluoropyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1,4-benzoxazine were reacted to yield N4-(1,4-Benzoxazin-7-yl)]-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) purity 94 % MS (m/e):281(MH^+).

7.1.119 N4-(1,4-Benzoxazin-3-on-6-yl)-N2-chloro-5-fluoropyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-1,4-benzoxazine-3-one were reacted to yield N4-(1,4-Benzoxazin-3-on-6-yl)-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H), 6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.73 (s, 2H) purity 96 % MS (m/e): 295 (MH^+).

7.1.120 N4-(1,4-Benzoxazin-3-on-7-yl)-N2-chloro-5-fluoropyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-1,4-benzoxazine-3-one were reacted to yield N4-(1,4-Benzoxazin-3-on-7-yl)-N2-chloro-5-fluoropyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.79 (m, 1H), 6.6 (m,1H), 4.68 (s, 2H) purity 93 % MS (m/e): 295 (MH^+).

7.1.121 N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-6-yl)-pyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-4-N-methyl-1,4-benzoxazine were reacted to yield N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-6-yl)-pyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) 2.8 (s, 3H) purity 95 % MS (m/e): 295 (MH^+).

7.1.122 N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-7-yl)-pyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-4-N-methyl -1,4-

benzoxazine were reacted to yield N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-7-yl)-pyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.05 (m, 2H), 3.2 (m, 2H) 2.8 (s, 3H) purity 94 % MS (m/e): 295 (MH^+).

7.1.123 N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-pyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-amino-4-N-methyl -1,4-benzoxazine-3-one were reacted to yield N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-6-yl)-pyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.73 (s, 2H) 2.8 (s, 3H) purity 96 % MS (m/e): 309 (MH^+).

7.1.124 N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-pyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 7-amino-4-N-methyl-1,4-benzoxazine-3-one were reacted to N2-Chloro-5-fluoro-N4-(N-methyl-1,4-benzoxazin-3-on-7-yl)-pyrimidineamine 1H DMSO 8.2 (d, 1H),6.8 (m, 1H), 6.75 (m, 1H), 6.60 (m,1H), 4.68 (s, 2H) 2.8 (s, 3H) purity 93 % MS (m/e): 309 (MH^+).

7.1.125 N2-chloro-N4-(3-ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoropyrimidinediamine (R909258) :

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 6-amino-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine were reacted to yield N2-chloro-N4-(3-ethylcarboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazin-6-yl)-5-fluoropyrimidinediamine 1H (DMSO-d6) 8.42 (s, 1H), 8.30 (m, 1H), , 8.05 (m, 1H), 7.43 (m, 1H), 5.53 (s, 2H), 4.25 (q, 2H J=6.5 Hz), 1.28 (t, 2H, J=6.5 Hz), purity 90 % MS (m/e): 390 (MH^+).

7.1.126 N2-Chloro-N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-pyrimidineamine

In like manner to 2-Chloro-N4-(3,4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine and 6-Amino-3,3-dimethyl-1,4-benzoxazine were reacted to yield N2-Chloro-N4-(3,3-dimethyl-1,4-benzoxazin-6-yl)-5-fluoro-pyrimidineamine 1H DMSO 8.18 (d, 1H), 6.8 (d, 1H), 6.67 (m, 2H), 3.76 (s, 2H), 1.05 (s, 6H) purity 99 % MS (m/e): 309 (MH^+)

7.1.127 2-Chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine (R935241)

In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 5-amino-1-(methoxycarbonyl)methyl-indazoline to produce 2-chloro-5-fluoro-N-[1-(methoxycarbonyl)methyl-indazoline-5-yl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): δ 10.04 (s, 1H), 8.28 (d, 1H, J = 3.5 Hz), 8.12 (s, 1H), 8.00 (dd, 1H, J = 1.2 and 4.1 Hz), 7.64 (d, 1H, J = 8.8 Hz), 7.58-7.54 (m, 1H), 5.39 (s, 2H), 3.66 (s, 3H).

7.1.128 2-Chloro-5-fluoro-N-[4*H*-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine (R935257)

In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 8-amino-4*H*-imidazo[2,1-*c*][1,4]-benzoxazine to produce 2-chloro-5-fluoro-N-[4*H*-imidazo[2,1-*c*][1,4]-benzoxazin-8-yl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d_6): ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.31 (s, 1H), 7.91 (d, 1H, J = 2.3 Hz), 7.74 (d, 1H, J = 1.2 Hz), 7.37 (dd, 1H, J = 2.3 and 8.8 Hz), 7.16 (d, 1H, J = 8.8 Hz), 7.14 (d, 1H, J = 1.2 Hz), 5.29 (s, 2H). LCMS: ret. time: 18.74 min.; purity: 99%; MS (*m/e*): 318 (MH^+).

7.1.129 2-Chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine (R935260)

In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 6-aminoindazole to produce 2-chloro-5-fluoro-N-(indazoline-6-yl)-4-pyrimidineamine . . ^{1}H NMR ($CDCl_3$): δ 13.03 (s, 1H), 10.07 (s, 1H), 8.32 (d, 1H, J = 3.5 Hz), 8.07 (s, 1H), 7.99 (s, 1H), 7.71 (d, 1H, J = 8.8 Hz), 7.34 (dd, 1H, J = 1.7 and 8.8 Hz). LCMS: ret. time: 18.52 min.; purity: 99%; MS (*m/e*): 263 (MH^+).

7.1.130 2-Chloro-5-fluoro-N-(indazoline-5-yl)-4-pyrimidineamine (R935265)

In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 5-aminoindazoline. ^{1}H NMR ($CDCl_3$): δ 9.99 (s, 1H), 8.26 (d, 1H, J = 3.5 Hz), 8.07 (s, 1H), 7.99 (d, 1H, J = 1.1 Hz), 7.53 (dd, 2H, J = 1.7 and 8.8 Hz). . LCMS: ret. time: 18.03 min.; purity: 97%; MS (*m/e*): 264 (MH^+).

7.1.131 2-Chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine (R935275)

In like manner to the preparation of 2-chloro-N-(3, 4-ethylenedioxyphenyl)-5-fluoro-4-pyrimidineamine, 2,4-dichloro-5-fluoropyrimidine was reacted with 1-aminopyrrole to produce 2-chloro-5-fluoro-N-(1H-pyrrol-1-yl)-4-pyrimidineamine. ^{1}H NMR ($CDCl_3$): δ 11.39 (s, 1H), 8.35 (d, 1H, J = 3.5 Hz), 6.83 (t, 2H, J = 2.3 Hz), 6.07 (t, 2H, J = 2.3 Hz). LCMS: ret. time: 18.95 min.; purity: 97%; MS (*m/e*): 213 (MH^+).

7.1.132 2-Chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853)

A reaction mixture containing 2,4-dichloro-5-fluoro-pyrimindine (1.2 equivalents) and 3-(tetrazol-5-yl)aniline (1 equivalents) in methanol:water (1:1; v/v) was heated at 60 °C for 24 h. Upon dilution with water and acidification, the solid formed was fitered, washed with water, dried and analyzed to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine (R926853). Alternatively this reaction can be achieved by treating 2,4-dichloro-5-fluoropyrimidine (1 equivalent) with 3-(tetrazol-5-yl)aniline (3 equivalents) in methanol:water (1:1; v/v) at 60 oC for 2-3 hours or at room temperature for 24 h to give 2-chloro-5-fluoro-N4-[3-(1H-tetrazol-5-yl)phenyl]-4-pyrimidineamine. ^{1}H NMR (DMSO-d6): δ 10.25 (s, 1H), 8.43 (s, 1H), 8.37 (d, 1H, J= 3.6 Hz), 7.90 (dd, 1H, J= 0.9 and 9 Hz), 7.75 (d, 1H, J= 7.5 Hz), 7.61 (t, 1H, J= 7.8 Hz); LCMS: purity: 90%; MS (m/e): 292 (MH^+).

7.1.133 2-Chloro-N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-2,4-pyrimidineamine (R950297)

A solution of 3,4-dihydro-4-hydroxy-6-amino-2H-1-benzopyran and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(4-hydroxy-3,4-dihydro-2H-1-benzopyran-6-yl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 99.3%; MS (m/e): 296.1 (MH^+).

7.1.134 2-Chloro-N4-(4-methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidineamine (R950375)

A solution of 3-(p-aminophenyl)-propionic acid and 2,4-diehloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(4-

methoxycarbonylethyleneoxyphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 93.3%; MS (m/e): 311.98 (M^-).

7.1.135 2-Chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine (R950298)

A solution of 3-carboxy-4-hydroxyaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-carboxy-4-hydroxyphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 87.4%; MS (m/e): 284.1 (MH^+).

7.1.136 2-Chloro-N4-(4-trifluoromethyl-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidineamine (R950390)

A solution of 4-trifluoromethyl-3-methoxycarbonylaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(4-trifluoromethyl-3-methoxycarbonylphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 96.4%; MS (m/e): 366.34 (MH^+).

7.1.137 2-Chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine (R950369)

A solution of 3-methylcarbonylaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-methylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 99.1%; MS (m/e): 266.12 (MH^+).

7.1.138 2-Chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine (R950370)

A solution of 3-phenylcarbonylaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-phenylcarbonylphenyl)-5-fluoro-2,4-pyrimidineamine as a pale brown solid. LCMS: purity: 78.5%; MS (m/e): 328.16 (MH^+).

7.1.139 2-Chloro-N4-(3-nitrophenyl)-5-fluoro-2,4-pyrimidineamine

A solution of 3-nitroaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-nitrophenyl)-5-fluoro-2,4-pyrimidineamine as a pale

brown solid. ^{1}H NMR (DMSO): δ 10.34 (s, 1H), 8.73 (d, 1H, J = 2.4 Hz), 7.66-8.29 (m, 4H).

7.1.140 2-Chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine (R950384)

A solution of 3-hydroxymethylen-4-methoxyaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-hydroxymethylen-4-methoxyphenyl)-5-fluoro-4-aminopyridine as a pale brown solid. LCMS: purity: 91.8%; MS (m/e): 266.03 (MH^-).

7.1.141 2-Chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine (R950387)

A solution of 3-amino-4-ethoxyaniline and 2,4-dichloro-5-fluoro-pyrimidine in MeOH was stirred for 2 hours at 70°C. The mixture was diluted with water and the resulting precipitate was filtered to give 2-chloro-N4-(3-amino-4-ethoxyphenyl)-5-fluoro-4-aminopyridine as a pale brown solid. LCMS: purity: 93.2%; MS (m/e): 252.06 (MH^-).

7.2 Synthesis of Amines and Amine Precursors

7.2.1 5-Amino-2-(2-hydroxyethyleneoxy)pyridine

A methanolic solution (50 mL) of 2-(2-hydroxyethyleneoxy)-5-nitropyridine (0.5 g) was hydrogenated in the presence of Pd/C (10%; 0.05 g) using a balloon filled with hydrogen for 2h. After the filtration through a pad of celite and washing with methanol the solution was concentrated to give the 5-amino-2-(2-hydroxyethyloxy)pyridine. ^{1}H NMR ($CDCl_3$): δ 7.58 (d, 1H, J= 3 Hz), 7.05 (dd, 1H, J= 2.7 and 8.1 Hz), 6.64 (d, 1H, J= 8.7 Hz), 4.36 (m, 2H), 3.89 (m, 2H).

7.2.2 4-Chloro-3-methoxyaniline

In like manner to the preparation of 5-amino-2-(2-hydroxyethyleneoxy)pyridine, the hydrogenation of 4-chloro-3-methoxynitrobenzene gave 4-chloro-3-methoxyaniline. LCMS: purity: 98%; MS: 199 (M+ acetonitrile).

7.2.3 2-[5-Amino-2-oxo-1,3-benzoxazol-3(2H)-yl]acetamide

In like manner to the preparation of 5-amino-2-(2-hydroxyethyleneoxy)pyridine, the hydrogenation of 2-[1,3-benzoxazol-2-oxo-5-nitro-3(2H)-yl)acetamide gave 2-[5-amino-2-oxo-1,3-benzoxazol-3(2H)-yl]acetamide. LCMS: purity: 96%; MS: 208 (MH^+).

7.2.4 7-nitro-1,2,3,4-tetrahydroisoquinoline

7-nitro-1,2,3,4-tetrahydroisoquinoline was prepared by nitration of 1,2,3,4-tetrahydroisoquinoline according to the following reference: Grunewald, Gary L.; Dahanukar, Vilas H.; Caldwell, Timothy M.; Criscione, Kevin R.; Journal of Medicinal Chemistry (1997), 40(25), 3997-4005.

7.2.5 2-(t-Butoxycarbonyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline

A mixture of 7-nitro-1,2,3,4-tetrahydroisoquinoline (0.55g, 3.1 mmole), di-t-butyldicarbonate (0.70g, 3.2 mmole), triethylamine (1.0 mL, 7.7 mmole) in dichloromethane (8 mL) was stirred at rt for 8h. The reaction mixture was diluted with water (50 mL) and stirred for 1h. The organic phase was separated and washed with brine. Concentration of the organic phase gave 2-(t-butoxycarbonyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline. ^1H NMR ($CDCl_3$): δ 8.03-7.95 (m, 2H), 7.28 (d, 1H, J= 8.4 Hz), 4.66 (s, 2H), 3.68 (t, 2H, J= 6.0 Hz), 2.92 (t, 2H, J= 6.0 Hz),1.49 (s, 9H).

7.2.6 2,3-Dihydro-6-nitro-4-benzypyranon

3-(p-Nitrophenyl)-propionic acid is dissolved in concentrated sulfuric acid and treated with P_2O_5. The mixture is stirred for 1 hr at room temperature and poured onto ice. Filtration gave 2,3-dihydro-6-nitro-4-benzypyranon as a white solid. ^1H NMR (DMSO): δ 8.47 (d, J = 3.0 Hz, 1H), 8.35 (dd, J = 3.0, 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 4.70 (t, J = 7.2 Hz, 1H), 2.90 (t, J = 7.2 Hz, 1H).

7.2.7 3,4-Dihydro-4-hydroxy-6-amino-2H-1-benzopyran

A mixture 2,3-dihydro-6-nitro-4-benzypyranon and Pd/C (10%) in MeOH was hydrogenated at 22°C for 3 hours (40psi). The mixture was filtered and concentrated to dryness to give 3,4-dihydro-4-hydroxy-6-amino-2H-1-benzopyran as a brown oil. ^1H NMR (DMSO): δ 6.40-6.56 (m, 3H), 5.05 (bs, 1H), 4.45 (bs, 1H), 3.94-4.09 (m, 2H), 1.76-1.98 (m, 2H).

7.2.8 N4-(3,4-Ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R950287)

A solution of 2-Chloro-5-ethoxycarbonyl-N4-(3,4-ethylenedioxyphenyl)-2,4-pyrimidineamine in EtOH was treated with a 25% aqueous solution of NH_3. The mixture was stirred for 30 min at 100°C and purified by flash chromatography on silica gel to give N4-(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.3%; MS (m/e): 317.28 (MH^+, 100).

7.2.9 3-(N-morpholinocarbonyl)aniline

To a 0°C solution of 3-nitrobenzoylchloride (0.50g, 2.7 mmole) and pyridine (0.27 mL, 3.2 mmole) in anhydrous dichloromethane (15 mL) was added morpholine (0.28 mL, 3.2 mmole). The reaction mixture was allowed to warm to rt and was stirred for 20h. The solvents were removed under vacuum and the residue suspended in ethyl acetate and washed with 1N HCl. The organic layer was washed with a saturated solution of $NaHCO_3$ and brine. Removal of the solvents under vacuum provided 1-(N-morpholinocarbonyl)-3-nitrobenzene which was used without further purification.

A mixture of 1-(N-morpholinocarbonyl)-3-nitrobenzene (0.64 g) and 10% Pd on activated carbon (60 mg) in degassed methanol (65 mL) was stirred under a balloon of H_2 for 2h. The reaction mixture was filtered through Celite® filter aid and then concentrated under reduced pressure to provide 3-(N-morpholinocarbonyl)aniline in quantitative yield. ^1H NMR ($CDCl_3$): δ 7.19-7.14 (m, 1H), 6.75-6.69 (m, 3H), 3.58-3.71 (m, 10H).

7.2.10 3-(N-propylcarbonyl)aniline

In like manner to the preparation of 3-(N-morpholinocarbonyl)aniline, 3-nitrobenzoylchloride and n-propylamine were reacted to prepare 1-[(N-propylamino)carbonyl]-3-nitrobenzene which underwent hydrogenation to provide 3-(N-propylcarbonyl)aniline. ^1H NMR ($CDCl_3$): δ 7.18 (t, 1H, J= 7.5 Hz), 7.13 (t, 1H, J= 1.8 Hz), 7.05-7.01 (m, 1H), 6.78 (ddd, 1H, J= 1.2, 2.4, and 7.5 Hz), 6.10 (bs, 1H), 3.58-3.53 (bs, 2H), 3.43-3.34 (m, 2H), 1.68-1.57 (m, 2H), 0.97 (t, 3H, J= 7.2 Hz).

7.2.11 3-[4-(Ethoxycarbonyl)piperidinocarbonyl]aniline

In like manner to the preparation of 3-(N-morpholinocarbonyl)aniline, 3-nitrobenzoylchloride and ethyl isonipecotate were reacted to prepare 1-[4-

(ethoxycarbonyl)piperidinocarbonyl]-3-nitrobenzene which underwent hydrogenation to provide 3-[4-(ethoxycarbonyl)piperidinocarbonyl]aniline.

7.2.12 3-(N-methylcarbonyl)aniline

In like manner to the preparation of 3-(N-morpholinocarbonyl)aniline, 3-nitrobenzoylchloride and methylamine hydrochloride were reacted to prepare 1-[(N-methylamino)carbonyl]-3-nitrobenzene which underwent hydrogenation to provide 3-(N-methylcarbonyl)aniline. ^{1}H NMR ($CDCl_3$): δ 7.18 (t, 1H, J= 7.5 Hz), 7.13 (t, 1H, J= 1.8 Hz), 7.04-6.99 (m, 1H), 6.81-6.75 (m, 1H), 6.05 (bs, 1H), 3.84 (bs, 2H), 2.99 (d, 3H, J= 4.8 Hz).

7.2.13 7-Amino-1-tetralone

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of 7-nitro-1-tetralone was carried out to prepare 7-amino-1-tetralone. ^{1}H NMR ($CDCl_3$): δ 7.32 (d, 1H, J= 2.4 Hz), 7.05 (d, 1H, J= 8.1 Hz), 6.82 (dd, 1H, J= 2.4 and 8.1 Hz), 2.85 (t, 2H, J= 6.6 Hz), 2.61 (t, 2H, J= 6.6 Hz), 2.14-2.04 (m, 2H).

7.2.14 7-Amino-2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of 2-(t-butoxycarbonyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline was carried out to prepare 7-amino-2-(t-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline. ^{1}H NMR ($CDCl_3$): δ 6.92 (d, 1H, J= 8.4 Hz), 6.52 (dd, 1H, J= 2.4 and 8.4 Hz), 6.44 (bs, 1H), 4.47 (s, 2H), 3.63-3.48 (m, 2H), 2.71 (t, 2H, J= 5.1 Hz), 1.45 (s, 9H).

7.2.15 7-Amino-1,2,3,4-tetrahydroisoquinoline

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of 7-nitro-1,2,3,4-tetrahydroisoquinoline was carried out to prepare 7-amino-1,2,3,4-tetrahydroisoquinoline. ^{1}H NMR (DMSO-d_6): δ 9.35 (bs, 1H), 6.82 (d, 1H, J= 8.1 Hz), 6.45 (dd, 1H, J= 2.4 and 8.4 Hz), 6.30 (d, 1H, J= 2.4 Hz), 5.05 (s, 2H), 4.05 (s, 2H), 3.24 (t, 2H, J= 6.6 Hz), 2.78 (t, 2H, J= 6.6 Hz).

7.2.16 2-(3-aminophenoxy)-N,2-dimethylpropanamide

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of N,2-dimethyl-2-(3-nitrophenoxy)propanamide was carried out to prepare 2-(3-

aminophenoxy)-N,2-dimethylpropanamide. ^{1}H NMR ($CDCl_3$): δ 7.03 (t, 1H, J= 7.8 Hz), 6.71 (bs, 1H), 6.39 (dd, 1H, J= 1.2 and 6.9 Hz), 6.29 (dd, 1H, J= 2.4 and 9.6 Hz), 6.25-6.22 (m, 1H), 2.86 (d, 3H, J= 4.2 Hz), 2.86 (d, 3H, J= 4.2 Hz), 1.50 (s, 6H).

7.2.17 Ethyl 2-(3-aminophenoxy)-2-methylpropanate

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of ethyl 2-methyl-2-(3-nitrophenoxy)propanate was carried out to prepare ethyl 2-(3-aminophenoxy)-2-methylpropanate. ^{1}H NMR ($CDCl_3$): δ 6.99 (t, 2H, J= 8.7 Hz), 6.32 (dt, 1H, J= 1.2 and 7.2 Hz), 6.24-6.18 (m, 2H), 4.23 (q, 2H, J= 7.2 Hz), 1.58 (s, 6H), 1.24 (t, 3H, J= 6.9 Hz).

7.2.18 N-methyl-2-(5-amino-2-methylphenoxy)acetamide

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of N-methyl-2-(2-methyl-5-nitrophenoxy)acetamide was carried out to prepare N-methyl-2-(5-amino-2-methylphenoxy)acetamide. ^{1}H NMR (CD_3OD): δ 6.86 (d, 1H, J= 7.5 Hz), 6.32-6.25 (m, 2H), 4.43 (s, 2H), 2.82 (s, 3H), 2.14 (s, 3H).

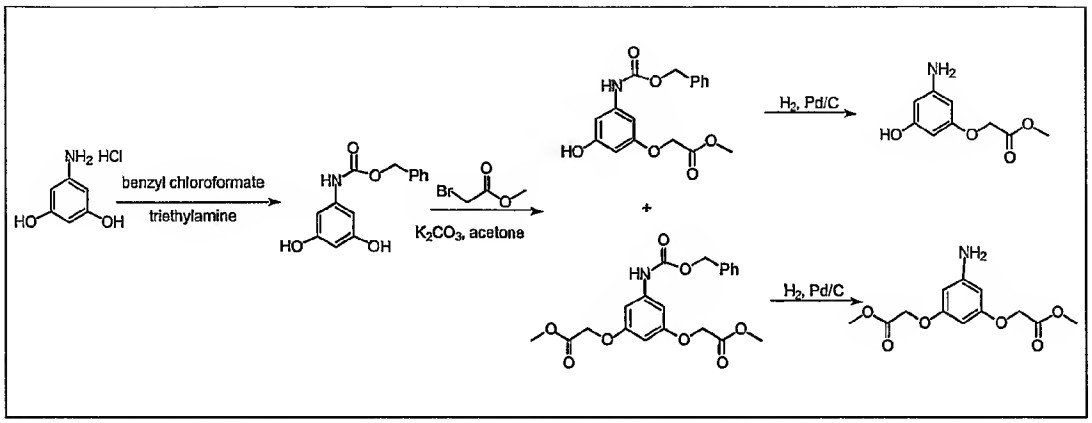
7.2.19 6-Amino-2-(methoxycarbonyl)-(1H)-indole

6-Amino-2-(methoxycarbonyl)-(1H)-indole was prepared according to the following references:

1. Adams, Richard E.; Press, Jeffery B.; Deegan, Edward G.; Synthetic Communications (1991), 12 (5), 675-681.

2. Boger, Dale L.; Yun, Weiya; Han, Nianhe; Johnson, Douglas S.; Biiorganic & Medicinal Chemistry (1995), 3(6), 611-621

7.2.20 Preparation of 3-hydroxy-5-(methoxycarbonylmethyleneoxy)aniline and 3,5-bis(methoxycarbonylmethyleneoxy)aniline



Benzyl N-(3,5-dihydroxyphenyl)carbamate

To a mixture of 5-aminobenzene-1,3-diol (0.60 g, 3.7 mmole) and sodium hydrogencarbonate (1.4 g, 16 mmole) in THF/water (15 mL, 1:1 v/v) was added dropwise benzyl chloroformate 1.6 mL, 11 mmole). After 3h at rt, THF was removed under vacuum and the remaining aqueous layer was extracted with ethyl acetate. Purification by column chromatograpy over silica gel provided benzyl N-(3,5-dihydroxyphenyl)carbamate. ^{1}H NMR (CD_3OD): δ 7.42-7.25 (m, 5H), 6.46 (d, 2H, J= 2.4 Hz), 5.97-5.94 (m, 1H), 5.14 (s, 2H).

Benzyl N-[3-hydroxy-5-(methoxycarbonylmethyleneoxy) phenyl]carbamate and Benzyl N-[3,5-bis(methoxycarbonyl methyleneoxy)phenyl]carbamate

In like manner to the preparation of ethyl 4-nitrophenoxyacetate, benzyl N-(3,5-dihydroxyphenyl)carbamate and methyl bromoacetate were reacted to give a mixture of benzyl N-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]carbamate ^{1}H NMR (DMSO-d_6): δ 9.62 (s, 1H), 9.44 (s, 1H), 7.42-7.31 (m, 5H), 6.63 (s, 1H), 6.50 (t, 1H, J= 2.4 Hz), 5.93 (t, 1H, J= 2.4 Hz), 5.10 (s, 2H), 4.63 (s, 2H), 3.67 (s, 3H),
and benzyl N-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]carbamate

^{1}H NMR ($CDCl_3$): δ 7.38-7.32 (m, 5H), 6.86 (s, 1H), 6.67 (d, 2H, J= 1.8 Hz), 6.19 (t, 1H, J= 2.4 Hz), 5.16 (s, 2H), 4.57 (s, 4H), 3.78 (s, 6H)

which were separated by column chromatograpy over silica gel.

3-Hydroxy-5-(methoxycarbonylmethyleneoxy)aniline

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of benzyl N-[3-hydroxy-5-(methoxycarbonylmethyleneoxy)phenyl]carbamate was carried out to prepare 3-hydroxy-5-(methoxycarbonylmethyleneoxy)aniline. ^{1}H NMR (CD_3OD): δ 5.87-5.80 (m, 2H), 5.78-5.72 (m, 1H), 4.56 (s, 2H), 3.76 (s, 3H).

3,5-Bis(methoxycarbonylmethyleneoxy)aniline

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of benzyl N-[3,5-bis(methoxycarbonylmethyleneoxy)phenyl]carbamate was carried out to prepare 3,5-bis(methoxycarbonylmethyleneoxy)aniline. ^{1}H NMR (CD_3OD): δ 5.92 (d, 2H, J= 2.4 Hz), 5.83 (t, 1H, J= 2.4 Hz), 4.58 (s, 4H), 3.78 (s, 6H).

7.2.21 N4-(3,4-Ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine (R950287)

A solution of 2-Chloro-5-ethoxycarbonyl-N4-(3,4-ethylenedioxyphenyl)-2,4-pyrimidineamine in EtOH was treated with a 25% aqueous solution of NH_3. The mixture was stirred for 30 min at 100°C and purified by flash chromatography on silica gel to give N4-(3,4-ethylenedioxyphenyl)-5-ethoxycarbonyl-2,4-pyrimidinediamine as a white solid. LCMS: purity: 92.3%; MS (m/e): 317.28 (MH^+, 100).

7.2.22 Ethyl 6-Nitro-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine

Was prepared according to J. of Heterocyclic Chemistry, **26,** 205, *(1989)*

7.2.23 Ethyl 6-Amino-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine

Ethyl 6-Nitro-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine was reduced shaken in MeOH under 40 p.s.i. H_2 with 20 weight percent of 10% Pd/C (Degussa) for 1 h then filtered and the solvent evaporated. The compound was purified directly by column chromatograph (EtOAc/hexane) to yield Ethyl 6-Amino-3-carboxy-4*H*-imidazo[5,1-*c*]-1,4-benzoxazine 1H (DMSO-d6) 8.41 (s, 1H), 6.98 (m, 1H), 6.82 (m, 1H), 6.43 (m, 1H), 5.28 ((s. 2H), 4.23 (q, 2H, J=6.2 Hz), 1.27 (t, 2H, J=6.2 Hz) purity 92 % MS (m/e): 232 (MH^+).

7.2.24 6-Amino-3,3-dimethyl-1,4-benzoxazine

A mixture of 15 g 2-Amino-4-nitrophenol and 40 g Boc_2O in 300 mL $CHCl_3$ was refluxed overnight filtered and the filtrate was evaporated to near dryness. The residue was

triturated with hexanes, collected by suction filtration, and dried to yield 2-N-Boc-amino-4-nitrophenol. The 2-N-Boc-amino-4-nitrophenol was refluxed in acetone with 15.6 mL of 1-Chloro-2-methylpropene and 25 g potassium carbonate overnight. The reaction mixture was poured into ice-slush, the solid was collected by suction filtration and washed with water. The solid was dissolved in EtOAc and the organic was washed with 10% NaOH solution, water, then brine and dried over $MgSO_4$. The organic was filtered to remove the drying agent and evaporated to yield 18 g 1-(2-N-Boc-amino-4-nitrophenoxy)-2-methyl-2-propene. 7.8 g of 1-(2-N-Boc-amino-4-nitrophenoxy)-2-methyl-2-propene was stirred overnight in methanolic HCl in a round-bottom flask with a septum wired on, and then heated with a reflux condenser attached at 80° C for 10 minutes. The reaction was cooled and the methanol was removed by rotary-evaporation. The residue was dissolved in 30 mL of 4N HCl, transferred to a new vessel to leave behind any undisolved solids and cooled to 0° C. 1.83 g of $NaNO_2$ in 5 mL water was added drop wise and the solution was neutralized with solid sodium bicarbonate. A solution of 1.64 g NaN_3 in 17 mL water was added slowly drop wise and the reaction was stirred 30 minutes. The precipitate was collected by suction filtration, washed well with water and dried on the funnel to yield 5.7 g 1-(2-Azido-4-nitrophenoxy)-2-methyl-2-propene. 7 g of 1-(2-Azido-4-nitrophenoxy)-2-methyl-2-propene was refluxed in 300 mL benzene overnight, cooled then evaporated. The crude product was recrystalized from EtOAc/Hexanes to yield 3-Methyl-6-nitro-azirino[2,1-*c*]-1,4-benzoxazine in two crops with a combined mass of 5.1 1 g of 3-Methyl-6-nitro-azirino[2,1-*c*]-1,4-benzoxazine was dissolved in 500 mL of MeOH/5% THF, 200 mg of 10% Pd/C (Degussa) was added and the resulting mixture was shaken under 30 p.s.i. H_2 atmosphere for 8 hours. The reaction mixture was filtered through a pad of celite and the solvent evaporated. The residue was dissolved in a minimum amount of DCM/THF/MeOH and loaded onto a 5 cm by 20 cm 3% MeOH/DCM SiO_2 column and the compound was eluted isocratically with a small amount of positive pressure. The appropriate fractions were combined and evaporated to yield 590 mg of 6-Amino-3,3-dimethyl-1,4-benzoxazine. 1H (DMSO-d6) 6.30 (d, 1H), 5.75 (d, 1H), 5.65 (dd, 1H), 3.58 (s, 2H), 1.08 (s, 6H) purity 99 % MS (m/e): 179 (MH^+).

7.2.25 Ethyl 4-Aminophenoxyacetate

Ethyl 4-Nitrophenoxyacetate

A dry reaction flask equipped with a reflux condenser, N_2 inlet and a magnetic stirring bar was charged with 3-nitrophenol (76.45 g, 550 mmol), K_2CO_3 (76.45 g, 550 mmol) and dry acetone (500 mL) under N_2 atmosphere. To this at room temperature was added ethyl bromoacetate (55.44 mL, 500 mmol) over a period of 15 min. The reaction mixture was refluxed for 16h, cooled and poured over ice-water (4 Kg). The resulting aqueous solution was extracted with CH_2Cl_2 (3 x 500 mL), dried over anhydrous Na_2SO_4 and solvent was removed to obtain 103g (92%) of the desired ethyl 4-nitrophenoxyacetate. ^1H NMR ($CDCl_3$): δ 8.20 (d, 2H, J= 8.2 Hz), 6.95 (d, 2H, J= 8.1 Hz), 4.72 (s, 2H), 4.25 (q, 2H), 1.23 (t, 3H); LCMS: ret. time: 27.07 min.; purity: 100%; MS: 267 (M+ acetonitrile).

Ethyl 4-Aminophenoxyacetate

A solution of ethyl 4-nitrophenoxyacetate (15 g) in EtOH (400 mL) was hydrogenated at 40 PSI for 40 minutes in the presence of 10% Pd/C (1.5 g, 10% by weight). After the filtration through a celite the solvent was removed under a reduced pressure to obtain ethyl 4-aminophenoxyacetate. ^1H NMR ($CDCl_3$): δ 6.77 (d, 2H, 8.1 Hz), 6.60 (d, 2H, J= 8.0 Hz), 4.50 (s, 2H), 4.24 (q, 2H), 1.24 (t, 3H); LCMS: ret. time: 12.00 min.; purity: 100%; MS (m/e): 196 (MH^+).

7.2.26 tert-Butyl 4-Aminophenoxyacetate

tert-Butyl 4-Nitrophenoxyacetate

In like manner to the preparation of ethyl 4-nitrophenoxyacetate, 4-nitrophenol and tert-butyl bromoacetate were reacted to prepare tert-butyl 4-nitrophenoxyacetate. ^1H NMR ($CDCl_3$): δ 8.2 (d, 2H, J= 8.1 Hz), 6.95 (d, 2H, J= 8.2 Hz), 4.60 (s, 2H), 1.42 (s, 9H).

tert-Butyl 4-Aminophenoxyacetate

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of tert-butyl 4-nitrophenoxyacetate was carried out to prepare tert-butyl 4-aminophenoxyacetate. ^1H NMR ($CDCl_3$): δ 6.74 (d, 2H, J= 9 Hz), 6.62 (d, 2H, J= 9 Hz), 4.42 (s, 2H), 1.42 (s, 9H); LCMS: ret. time: 16.35 min.; purity: 94%; MS (m/e): 224 (MH^+).

7.2.27 Ethyl 3-Aminophenoxyacetate

Ethyl 3-Nitrophenoxyacetate

In like manner to the preparation of ethyl 4-nitrophenoxyacetate, 3-nitrophenol and ethyl bromoaeetate were reacted to prepare ethyl 3-nitrophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 7.88 (dt, 1H, J= 1.2 and 8.7 Hz), 7.71 (t, 1H, J= 2.4 Hz), 7.45 (t, 1H, J= 8.4 Hz), 7.27 (dt, 1H, J= 2.4 and 8.4 Hz), 4.70 (s, 2H), 4.29 (q, 2H, J= 6.9 Hz), 1.30 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 27.28 min.; purity: 96%.

Ethyl 3-Aminophenoxyacetate

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of ethyl 3-nitrophenoxyacetate was carried out to prepare ethyl 3-aminophenoxyacetate. ^{1}H NMR ($CDCl_3$): δ 7.05 (t, 1H, J= 7.2 Hz), 6.30 (m, 3H), 4.56 (s, 2H), 4.25 (q, 2H, J= 7.2 Hz), 1.29 (t, 3H, J= 6.9 Hz); LCMS: ret. time: 10.69 min.; purity: 96%; MS (m/e): 196 (MH^+).

7.2.28 (±)-Ethyl 2-(4-Aminophenoxy)propionate

In like manner to the preparation of ethyl 4-aminophenoxyacetate, hydrogenation of ethyl (±)-2-(4-nitrophenoxy)propionate was carried out to prepare (±) ethyl 2-(4-aminophenoxy)propionate. ^{1}H NMR ($CDCl_3$): δ 6.70 (d, 2H), 6.58 (d, 2H), 4.60 (m, 1H), 4.20 (q, 2H), 3.2 (bs, 2H), 1.45 (d, 3H), 1.22 (t, 3H).

7.2.29 N-Methyl 3-Aminophenoxyacetamide

N-Methyl 3-Nitrophenoxyacetamide

A mixture of ethyl 3-nitrophenoxyacetate (9.12g, 40 mmol), methylamine hydrochloride (26.8g, 400 mmol) and diisopropylethylamine (35.5 mL, 200 mL) in MeOH (100 mL) was stirred in a pressure vial at 90 °C for 6h. The reaction was cooled to room temperature, diluted with water (1 liter), the solid formed was filtered, washed with water and dried to get the desired N-methyl 3-nitrophenoxyacetamide (8g, 95%). ^{1}H NMR $CDCl_3$): δ 7.91 (dd, 1H, J= 1.8 and 8.1 Hz), 7.78 (t, 1H, J= 2.4 Hz), 7.50 (t, 1H, J= 8.7 Hz), 7.29 (dd, 1H, J= 1.8 and 8.4 Hz), 6.50 (bs, 2H), 4.57 (s, 2H), 2.95 and 2.93 (2s, 3H); LCMS: ret. time: 17.54 min.; purity: 100%; MS (m/e): 211 (MH^+).

N-Methyl 3-Aminophenoxyacetamide

In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of N-methyl 3-nitrophenoxyacetamide (8 g, 39 mmol) was conducted to give the desired N-methyl 3-aminophenoxyacetamide (6g, 86%). ^{1}H NMR (CD_3OD): δ 6.99 (t, 1H, J= 8.1 Hz), 6.37-6.25 (m, 3H), 4.41 (s, 2H), 2.80 (s, 3H); LCMS: ret. time: 19.80 min.; purity: 100%.

7.2.30 2-Methoxycarbonyl-5-aminobenzofuran (R926610)

2-Methoxycarbonyl-5-nitrobenzofuran (R926609)

To a suspension of 5-nitro-2-benzofurancarboxylic acid (5 g, 24.15 mmol) in CH_2Cl_2 (250 mL) at 0 °C was added DMF (0.100 mL) followed by $(COCl)_2$ (2M in CH_2Cl_2, 36.23 mL, 72.46 mL) over a period of 10 min. The reaction was stirred at 0 °C for 1h and then at room temperature for 30 min. The reaction solvent was removed under a reduced pressure, dried under high vacuum and again suspended in CH_2Cl_2 (250 mL). The solution was cooled to 0 °C, were added pyridine (4.8 mL, 48.03 mmol) followed by MeOH (10 mL, excess) and stirred overnight. The extractive work-up with CH_2Cl_2 gave the expected 2-methoxycarbonyl-5-nitrobenzofuran (**R926609**). ^{1}H NMR ($CDCl_3$): δ 8.66 (d, 1H, J= 2.4 Hz), 8.36 (dd, 1H, J= 2.4 and 9.6 Hz), 7.71 (d, 1H, J= 9.3 Hz), 7.65 (s, 1H), 4.01 (s, 3H); LCMS: ret. time: 26.94 min.

2-Methoxycarbonyl-5-aminobenzofuran (R926610)

In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of 2-methoxycarbonyl-5-nitrobenzofuran (2 g) in MeOH gave 2-methoxycarbonyl-5-aminobenzofuran. ^{1}H NMR ($CDCl_3$): δ 7.38 (bt, 2H), 6.90 (bd, 1H), 6.85 (bdd, 1H), 3.98 (s, 3H).

7.2.31 Methyl 2-(2-methyl-5-nitrophenoxy)acetate

In like manner to the preparation of ethyl 4-nitrophenoxyacetate, 2-methyl-5-nitrophenol and methyl bromoacetate were reacted to prepare methyl 2-(2-methyl-5-nitrophenoxy)acetate. ^{1}H NMR (CD_3OD): δ 7.80 (dd, 1H, J= 2.4 and 8.1 Hz), 7.65 (d, 1H, J= 2.4 Hz), 7.38 (d, 1H, J= 8.1 Hz), 4.90 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H).

7.2.32 Ethyl 2-methyl-2-(3-nitrophenoxy)propanate

A mixture of 3-nitrophenol (0.50g, 3.6 mmole), ethyl bromodimethylacetate (0.64g, 3.3 mmole), K_2CO_3 (1.3 g, 9.4 mmole), potassium iodide (catalytic) in absolute ethanol (8 mL) was heated at 70°C for 18h. The reaction mixture was cooled, poured into a saturated solution of NaHCO3, and extracted with dichloromethane. The product, ethyl 2-methyl-2-(3-nitrophenoxy)propanate, was obtained after purification by column chromatography over silica gel. ^{1}H NMR ($CDCl_3$): δ 7.85 (dt, 1H, J= 1.2 and 8.1 Hz), 7.68 (t, 1H, J= 2.4 Hz), 7.40 (t, 1H, J= 8.4 Hz), 7.19-7.13 (m, 1H), 4.26 (q, 2H, J= 7.2 Hz), 1.64 (s, 6H), 1.26 (t, 3H, J= 7.21),

7.2.33 N-Methyl-2-(2-methyl-5-nitrophenoxy)acetamide

In like manner to the preparation of N-methyl 3-nitrophenoxyacetamide, methyl 2-methyl-5-nitrophenoxyacetate and methylamine hydrochloride were reacted to prepare N-methyl-2-(2-methyl-5-nitrophenoxy)acetamide. ^{1}H NMR (CD_3OD): δ 7.82 (dd, 1H, J= 2.4 and 8.1 Hz), 7.69 (d, 1H, J= 2.4 Hz), 7.40 (d, 1H, J= 8.1 Hz), 4.66 (s, 2H), 2.83 (s, 3H), 2.40 (s, 3H).

7.2.34 N,2-Dimethyl-2-(3-nitrophenoxy)propanamide

In like manner to the preparation of ethyl 2-methyl-2-(3-nitrophenoxy)propanate, 3-nitrophenol and N,2-dimethyl-2-bromopropanamide (prepared according to the following reference: Guziec, Frank S., Jr.; Torres, Felix F. Journal of Organic Chemistry (1993), 58(6), 1604-6) were reacted to prepare N,2-dimethyl-2-(3-nitrophenoxy)propanamide. ^{1}H NMR ($CDCl_3$): δ 7.94 (dt, 1H, J= 1.2 and 8.1 Hz), 7.78 (t, 1H, J= 2.4 Hz), 7.45 (t, 1H, J= 8.4 Hz), 7.22 (ddd, 1H, J= 1.2, 2.4, and 8.1 Hz), 6.61 (bs, 1H), 2.89 (d, 3H, J= 5.1 Hz), 1.55 (s, 6H).

7.2.35 4-Amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene

4-Nitro-[(1H,1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene

A mixture of 2-cyanomethoxy-4-nitrophenyl (5.8 g, 32.6 mmol), sodium azide (6.3 g, 98.0 mmol) and ammonium chloride (8.5 g, 163.3 mmol) was suspended in DMF (100 mL) containing acetic acid (1 mL) and the mixture heated at 70 °C. After 17 h, the reaction was cooled to room temperature and 2 N aqueous hydrochloric acid (100 mL) was added.

The solid which precipitated out of the reaction mixture was collected by filtration, washed with water (2 x 20 mL) then hexane (30 mL), affording compound 4-nitro-[(1H,1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (6.7 g, 99%) as an orange solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.25 (d, J = 9.2 Hz, 2H), 7.29 (d, J = 9.1 Hz, 2H), 5.68 (s, 2H); ESI MS *m/z* 220 [$C_8H_7N_5O_3$ - H]$^-$.

4-Amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene

A mixture of 4-nitro-[(1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (6.7 g, 30.4 mmol) and 5 wt % palladium on carbon (700 mg) suspended in ethanol/concentrated hydrochloric acid (14:1, 150 mL) was hydrogenated in a sealed vessel at 50 psi. The mixture was shaken until no further hydrogen uptake was observed, after which the reaction was filtered through diatomaccous earth with chloroform and the filtrate concentrated to afford crude product. Purification by flash chromatography (7:2.5:0.5 $CHCl_3/CH_3OH/NH_4OH$) afforded 4-amino-[(1H,1,2,3,4-tetrazolyl)methyleneoxy)]benzene as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.76 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 8.7 Hz, 2H), 5.07 (s, 2H); ESI MS *m/z* 190 [$C_8H_9N_5O$ - H]$^-$.

7.2.36 4-Amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene

4-Nitro-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene and 4-Nitro-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene

A mixture of 4-nitro-[(1H,1,2,3,4-tetrazolyl)methyleneoxy]benzene (10.00 g, 45.2 mmol), cesium carbonate (22.09 g, 67.8 mmol) and methyl iodide (7.70 g, 54.3 mmol) in DMF (200 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated to remove most of the DMF and the crude residue was partitioned between chloroform (100 mL) and water (50 mL). The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated to afford crude product as a orange solid. Purification by flash chromatography (chloroform) afforded 4-nitro-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (d, J = 9.2 Hz, 2H), 7.31 (d, J = 9.2 Hz, 2H), 5.72 (s, 2H), 4.15 (s, 3H); and 4-nitro-(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (d, J = 9.3 Hz, 2H), 7.29 (d, J = 9.3 Hz, 2H), 5.58 (s, 2H), 4.41 (s, 3H).

4-Amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene

A mixture of 4-nitro-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene (3.60 g, 15.3 mmol) and 5% Pd/C (0.40 g) in 14:1 ethanol/concentrated hydroehloric acid (75 mL) was shaken at room temperature in a atmosphere of hydrogen at 50 psi. After 4 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with a 6:3:1 chloroform/methanol/concentrated ammonium hydroxide solution and the filtrate concentrated to afford crude 4-amino-[(1-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]-benzene, which was purified by flash chromatography (95:5 chloroform/ methanol): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (br s, 2H), 6.79 (d, J = 6.9 Hz, 2H), 6.55 (d, J = 6.9 Hz, 2H), 5.36 (s, 2H), 4.10 (s, 3H).

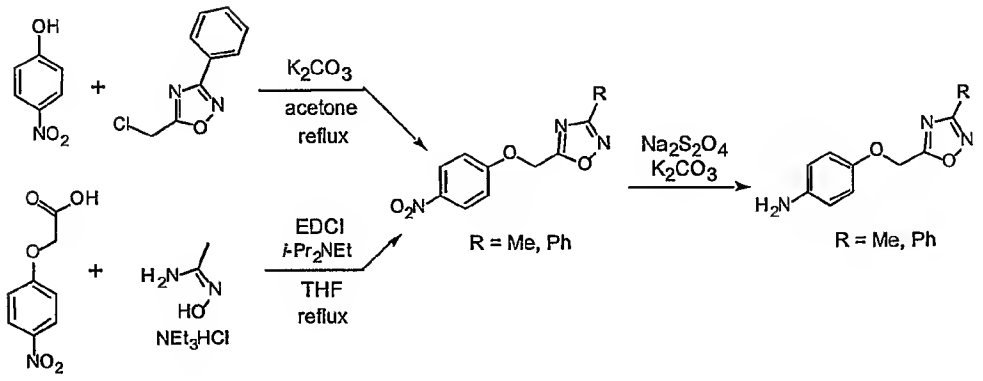
7.2.37 4-Amino-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene

A mixture of 4-nitro-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene (3.60 g, 15.3 mmol) and 5% Pd/C (0.40 g) in 14:1 ethanol/concentrated hydrochloric acid (75 mL) was shaken at room temperature in a hydrogen atmosphere at 50 psi. After 3 h no further hydrogen uptake was observed. The reaction mixture was filtered through diatomaceous earth, the solids washed with a 6:3:1 chloroform/methanol/concentrated ammonium hydroxide solution and the filtrate concentrated to afford crude 4-amino-[(2-methyl-1,2,3,4-tetrazol-5-yl)methyleneoxy]benzene, which was purified by flash chromatography (95:5 chloroform/ methanol): ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.80 (br s, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.50 (d, J = 9.0 Hz, 2H), 5.17 (s, 2H), 4.37 (s, 3H).

7.2.38 2-Ethoxycarbonyl-5-aminoindole (R926611)

In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of 2-ethoxycarbonyl-5-nitroindole gave the 2-ethoxycarbonyl-5-aminoindol. LCMS: ret. time: 13.44 min.; purity: 93%; MS (m/e): 205 (MH^+).

7.2.39 5-[(4-Aminophenoxy)methyl]-3-phenyl-1,2,4-oaxadiazole



Preparation of 5-[4-(Nitrophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole

4-Nitrophenol (0.36 g, 2.56 mmole), 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (0.5 g, 2.56 mmole) and anhydrous K_2CO_3 (0.39 g, 2.82 mmole) were dissolved in anhydrous acetone (20 mL) and heated to reflux for 12 h. Reaction mixture was cooled and the solvent removed under vacuum. The crude solid formed was collected by filtration, washed with water and dried under vacuum to provide 5-[(4-nitrophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole (0.70 g, 92%). ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 2H, J= 8.8 Hz), 8.08 (dd, 2H, J= 8.2 Hz), 7.52-7.49 (m, 3H), 7.13 (d, 2H, J= 8.8 Hz), 5.45 (s, 2H).

Preparation of 5-[(4-Aminophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole

The 5-[(4-nitrophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole (0.5 g, 1.68 mmole) was dissolved in methanol:methylenechloride (1:1) (120 mL). Aqueous solution of (15 mL) sodium hydrosulfite (0.88g, 5.05 mmole) and K_2CO_3 (0.70g, 5.06 mmole) was added dropwise under nitrogen for 10 min. The contents were allowed to stir at room temperature. After consumption of starting material, reaction mixture was concentrated, diluted with water till the homogeneous layer formed. The aqueous layer was extracted with several times with ethylacetate and methylene chloride. The turbid organic layers were combined, dried with anhydrous Na_2SO_4 and concentrated. Purification of the solid concentrate by silica gel chromatography provided 5-[(4-aminophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole (0.23g, 51%). ^{1}H NMR ($CDCl_3$): δ 8.11 (m, 2H), 7.52-7.46 (m, 3H), 6.87 (d, 2H, J= 8.8 Hz), 6.64 (d, 2H, J= 8.8 Hz), 5.26 (s, 2H), 3.49 (br s, 2H).

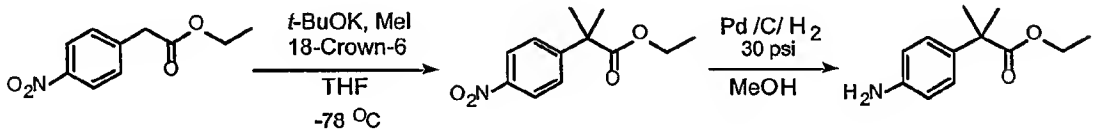
Preparation of 5-[(4-Nitrophenoxy)methyl]-3-methyl-1,2,4-oxadiazole

A mixture of 4-nitrophenoxy acetic acid (2.25 g, 11.4 mmole), acetamideoxime, triethylamine hydrochloride (3.85g, 27.62 mmole), EDCI.HCl (4.37g, 22.79 mmole) and diisopropylethylamine (7.42g, 57.40 mmole) in anhydrous THF (250 ml) was refluxed for 18h. The unhomogenous brown colored reaction mixture was quenched with water and extracted with EtOAc (3 x 300 mL). The combined organic layers washed successively with aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Removal of solvent and purified by chromatographic purification provided 5-[(4-nitrophenoxy)methyl]-3-methyl-1,2,4-oxadiazole (1.62 g, 60 %). ^1H NMR ($CDCl_3$): δ 8.24 (d, 2H, J= 8.8 Hz), 7.08 (d, 2H, J= 8.8 Hz), 5.36 (s, 2H), 2.44 (s, 3H).

Preparation of 5-[(4-Aminophenoxy)methyl]-3-methyl-1,2,4-oxadiazole

In like manner to the preparation of 5-[(4-aminophenoxy)methyl]-3-phenyl-1,2,4-oxadiazole, 5-(4-nitrophenoxymethyl)-3-methyl-1,2,4-oxadiazole was reacted with aqueous solution of sodium hydrosulfite and K_2CO_3 to prepare 5-[(4-aminophenox)ymethyl]-3-methyl-1,2,4-oxadiazole. ^1H NMR ($CDCl_3$): δ 6.82 (d, 2H, J= 8.8 Hz), 6.63 (d, 2H, J= 8.8 Hz), 5.15 (s, 2H), 3.38 (br s, 2H), 2.41 (s, 3H).

7.2.40 Ethyl 2-(4-aminophenyl)-2-methylpropionate



Ethyl 2-methyl-2-(4-nitrophenyl)propionate

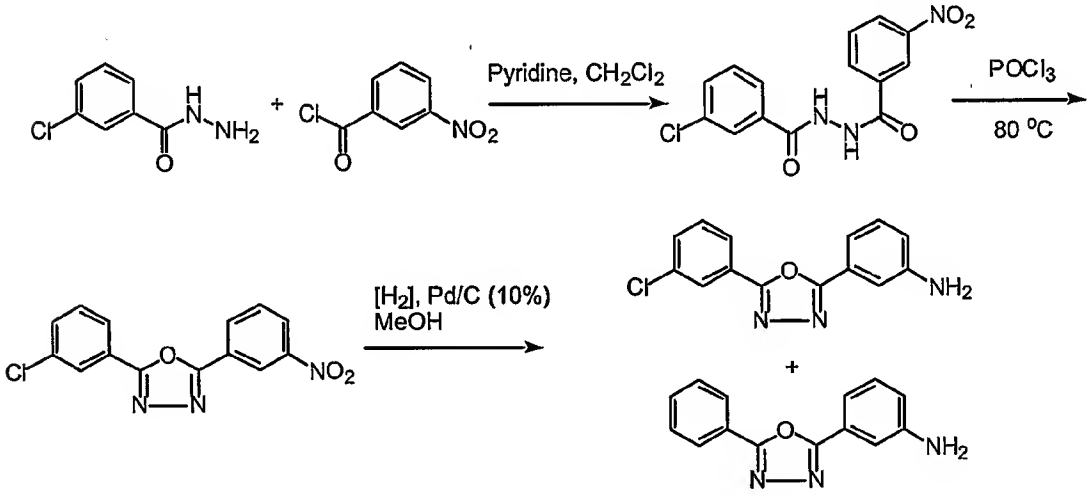
A dry reaction flask charged with ethyl 4-nitrophenylacetate (5.0 g, 23.89 mmole), iodomethane (8.48 g, 3.72 mL, 59.74 mmole), 18-crown-6 (1.57 g, 5.93 mmole) in dry THF (200 mL) was cooled to –78 °C under nitrogen atmosphere. While stirring the contents, *t*-BuOK (5.90 g, 52.57 mmole) was added portionwise. The resulting violet preeipitate was stirred at –78 °C for 2h and allowed the contents to warm to room temperature. The reaction was stirred at room temperature for 6h. At this time, once again the contents were cooled to –78 °C another portion of iodomethane, *t*-BuOK, and 18-crown-6 were added successively and stirred at the same temperature for 2h. The reaction was allowed to warm

to room temperature and stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (75 mL), the resulting homogenous mixture extracted with ether (4 x 200 mL), dried over anhydrous Na_2SO_4, and concentrated. The concentrate was purified by silica gel column chromatography with 1%EtOAc/hexanes to provide ethyl 2-methyl-2-(4-nitrophenyl)propionate as a pale yellow oil (2.38, 42%).. ^1H NMR ($CDCl_3$): δ 8.17 (d, 2H, J= 8.8 Hz), 7.49 (d, 2H, J= 8.8 Hz), 4.12 (qt, 2H, J= 7.0 Hz), 1.60 (s, 6H), 1.17 (t, 3H, J= 7.0 Hz).

Ethyl-2-(4-aminophenyl)-2-methylpropionate

In like manner to the preparation of ethyl 4-aminophenoxyacetate, the hydrogenation of ethyl 2-methyl-2-(4-nitrophenyl)propionate provided ethyl-2-(4-aminophenyl)-2-methylpropionate. ^1H NMR ($CDCl_3$): δ 7.16 (d, 2H, J= 8.8 Hz), 6.63 (d, 2H, J= 8.8 Hz), 4.09 (qt, 2H, J= 7.0 Hz), 3.62 (br s, 2H), 1.52 (s, 6H), 1.17 (t, 3H, J= 7.0 Hz).

7.2.41 Anilines substituted with 1,3,4-oxadiazole moieties



N'1-(3-Chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide

To a solution of 3-chlorobenzohydrazide (1 equivalent) and pyridine (2 equivalents) in CH_2Cl_2 at 0 °C was added a CH_2Cl_2 solution of 3-nitrobenzoyl chloride (1 equivalents) and stirred at 0 °C for 1 h and then at room temperature for overnight. The resulting solution was concentrated and diluted with water, basified with $NaHCO_3$, the solid was filtered, washed with water, dried and analyzed to obtain N'1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide. ^1H NMR (DMSO-d6): δ 10.99 (s, 1H), 10.79 (s, 1H), 8.73 (bs, 1H), 8.43 (bdd, 1H, J= 1.2 and 8.1 Hz), 8.33 (bdd, 1J, J= 8.4 Hz), 7.95 (s, 1H), 7.87 (m,

2H), 7.67 (bdd, 1H, J= 1.2 and 8.1 Hz), 7.57 (t, 1H, J= 7.8 Hz); LCMS: purity: 85%; MS (m/e): 320 (MH^+).

[2-(3-Chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene

A suspension of N'1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide (0.321 g) in $POCl_3$ (3 mL) was stirred at 90 °C for 24 h. The resulting clear solution was quenched with ice-water, solid obtained was filtered washed with water, dried and analyzed to give [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene. ^1H NMR (DMSO-d6): δ 8.86 (t, 1H, J= 1.8 Hz), 8.59 (dt, 1H, J= 1.8 and 8.4 Hz), 8.48 (m, 1H), 8.25 (t, 1H, J= 1.8 Hz), 8.16 (dt, 1H, J= 1.2 and 7.5 Hz), 7.93 (t, 1H, J= 8.1 Hz), 7.75 (m, 1H), 7.66 (t, 1H, J= 7.5 Hz), LCMS: purity: 86%; MS (m/e): 302 (MH^+).

Reduction of [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene

The hydrogenation of [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene (0.2 g) using 10% Pd/C (0.04 g) in MeOH (200 mL) at 15 PSI for 1 h gave a mixture of two products viz. 3-amino-[2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]benzene and 3-amino-(2-phenyl-1,3,4-oxadiazol-5-yl)benzene which were separated by silica gel column chromatography using n-hexanes then n-hexanes: 5-10% EtOAc as a solvent system. **3-Amino-[2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]benzene:** ^1H NMR (DMSO-d6): δ 8.08 (m, 2H), 7.64 (m, 4H), 7.42 (m, 1H), 7.10 (m, 1H); LCMS: purity: 82%; MS (m/e): 272 (MH^+). **3-Amino-(2-phenyl-1,3,4-oxadiazol-5-yl)benzene:** ^1H NMR (DMSO-d6): δ 8.13 (m, 1H), 7.54 (m, 5H), 7.30 (m, 1H), 6.86 (dd, 1H, J= 1.5 and 8.1 Hz); LCMS: purity: 93%; MS (m/e): 238 (MH^+).

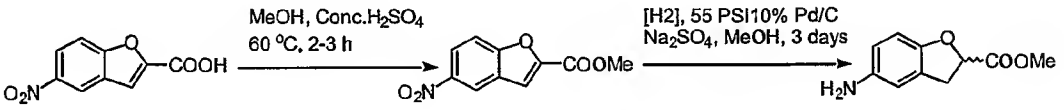
N'1-(Ethoxycarbonylmethylenecabonyl)-3-nitrobenzene-1-carbohydrazide

In like manner to the preparation of N' 1-(3-chlorobenzoyl)-3-nitrobenzene-1-carbohydrazide, the reaction of 3-nitrobenzoyl chloride with ethoxycarbonylmethlenecarbohydrazide gave N'1-(ethoxycarbonylmethylenecabonyl)-3-nitrobenzene-1-carbohydrazide. ^1H NMR (CD_3OD): δ 8.74 (m, 1H), 8.44 (dd, 1H, 1.8 and 8.1 Hz), 8.25 (bd, 1H, J= 8.4 Hz), 7.76 (t, 1H, J= 8.4 Hz), 4.22 (q, 2H, J= 6.9 Hz), 3.44 (bs, 2H), 1.29 (t, 3H, J= 6.8 Hz); LCMS: purity: 93%; MS (m/e): 296 (MH^+).

[2-(Ethoxycarbonylmethylene)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene

In like manner to the preparation of [2-(3-chlorophenyl)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene the reaction of POCl3 with N'1-(ethoxycarbonylmethylenecabonyl)-3-nitrobenzene-1-carbohydrazide gave [2-(ethoxycarbonylmethylene)-1,3,4-oxadiazol-5-yl]-3-nitrobenzene. ^{1}H NMR ($CDCl_3$): δ 8.88 (t, 1H, J= 1.8 Hz), 8.42 (m, 2H), 7.74 (t, 1H, J= 7.5 Hz), 4.27 (q, 2H, J= 7.2 Hz), 4.08 (s, 2H), 1.31 (t, 3H, J= 7.2 Hz); LCMS: purity: 95%; MS (m/e): 278 (MH^+).

7.2.42 Synthesis of (±)-5-Amino-(2,3-dihydro-2-methoxycarbonyl)benzofuran



2-Methoxycarbonyl-5-nitrobenzofuran

A mixture of 2-carboxy-5-nitrobenzofuran (2.0 g), MeOH (10 mL) and Concentrated H_2SO_4 (2.1 mL) was heated in a sealed tube at 60 °C for 3 h. Upon cooling to the room temperature it was quenched with ice-water and carefully basified with addition of $NaHCO_3$. The solid obtained was filtered, washed with water, dried and analyzed to give 2-methoxycarbonyl-5-nitrobenzofuran. ^{1}H NMR ($CDCl_3$): δ 8.66 (d, 1H, J= 2.4 Hz), 8.36 (dd, 1H, J= 2.4 and 9.6 Hz), 7.71 (d, 1H, J= 9.3 Hz), 7.65 (s, 1H), 4.01 (s, 3H); LCMS: purity: 97%; MS (m/e): 222 (MH^+).

(±)-5-Amino-(2,3-dihydro-2-methoxycarbonyl)benzofuran

A suspension of 2-methoxycarbonyl-5-nitrobenzofuran (2.0 g), 10% Pd/C (2.0 g), Na_2SO_4 (2.0 g) in MeOH (500 mL) was hydrogenated at 55 PSI for 3 days. The resulting solution was filtered through a pad of celite, concentrated and chromatographed using n-hexanes then 10%, 20% EtOAc/n-hexanes to give (±)-5-amino-(2,3-dihydro-2-methoxycarbonyl)benzofuran. ^{1}H NMR ($CDCl_3$): δ 6.69 (d, 1H, J= 8.1 Hz), 6.56 (d, 1H, J= 1.2 Hz), 6.48 (dd, 1H, J= 1.8 and 7.5 Hz), 5.14 (dd, 1H, J= 6.6 and 7.2 Hz), 3.79 (s, 3H), 3.47 (dd, 1H, J= 10.5 and 10.8 Hz), 3.26 (dd, 1H, J= 7.2 and 6.6 Hz); LCMS: purity: 100%; MS (m/e): 194 (MH^+).

7.2.43 3-[1-Bis(ethoxycarbonyl)ethoxy]aniline

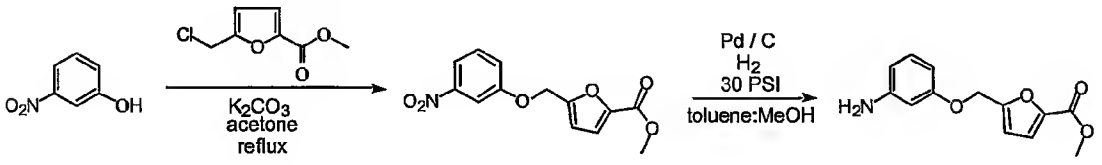
Preparation of Diethyl 2-methyl-2-(3-nitrophenoxy)malonate

Diethyl 2-bromo-2-methylmalonate (1.0 g, 3.95 mmole) was added to a stirred suspension of potassium fluoride (0.57 g, 9.8 mmole) in dry DMF (5 mL). After stirring for 20 min at room temperature, 3-nitrophenol (0.55 g, 3.95 mmole) was added. The resulting mixture was stirred at 60 ^{o}C for 6 h, cooled to room temperature, diluted with water (30 mL) and extracted with ethyl acetate (3 X 200 mL). The organic layer was washed with aq.1N NaOH (2 X 75 mL), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to provide diethyl 2-methyl-2-(3-nitrophenoxy)malonate (0.89 g, 80%). ^{1}H NMR ($CDCl_3$): δ 7.92 (dd, 1H, J = 2.3 and 8.2 Hz), 7.82 (t, 1H, J = 2.3 Hz), 7.41 (t, 1H, J = 8.2 Hz), 7.30 (dd, 1H, J = 2.3 and 8.2 Hz), 4.28 (qt, 4H, J = 7.0 Hz), 1.81 (s, 3H), 1.26 (t, 6H, J = 7.0 Hz).

Preparation of 3-[1-Bis(ethoxycarbonyl)ethoxy]aniline

Diethyl 2-methyl-2-(3-nitrophenoxy)malonate (0.75 g, 2.40 mmole) was dissolved in toluene: ethanol (1:1, 100 mL), transferred to par shaker bottle containing Pd/C (0.15 g) and anhydrous Na_2SO_4 (5.0 g) in the presence of nitrogen atmosphere. The resulting mixture was treated with hydrogen (30 PSI) till the disappearance of diethyl 2-methyl-2-(3-nitrophenoxy)malonate (2 h). The mixture was filtered through celite covered with anhydrous Na_2SO_4 followed by washing the celite pad with EtOAc. The filtrated was concentrated and dried under vacuo to furnish 3-[1-bis(ethoxycarbonyl)ethoxy]aniline in quantitative yield . ^{1}H NMR ($CDCl_3$): δ 6.98 (t, 1H, J = 8.2 Hz), 6.37-6.28 (m, 3H), 4.26 (qt, 4H, J = 7.0 Hz), 3.65 (br s, 2H), 1.72 (s, 3H), 1.24 (t, 6H, J = 7.0 Hz).

7.2.44 Preparation of 4-(4-aminophenoxymethyl)-2-methoxycarbonyl-furan



Preparation of 4-(4-nitrophenoxymethyl)-2-methoxycarbonyl-furan

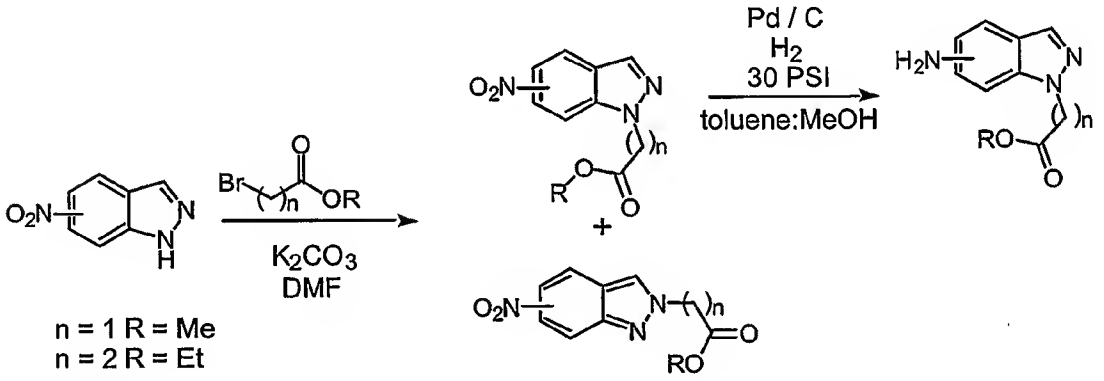
3-Nitrophenol (1.0 g, 7.19 mmole), methyl 5-(chloromethyl)-2-furoate (1.38 g, 7.90 mmole) and anhydrous K_2CO_3 (1.19 g, 8.60 mmole) in acetone (30 mL) were refluxed for 8

h. The reaction mixture was cooled and diluted with water. The resultant white solid was filtered, washed with water and air dried overnight to give 1.81 g (90%) of the desired product. ^{1}H NMR ($CDCl_3$): δ 7.86 (dd, 1H, J = 2.3 and 8.2 Hz), 7.80 (t, 1H, J = 2.3 Hz), 7.45 (t, 1H, J = 8.2 Hz), 7.27 (dd, 1H, J = 2.3 and 8.2 Hz), 7.17 (d, 1H, J = 3.5 Hz), 6.58 (d, 1H, J = 3.5 Hz), 5.13 (s, 2H), 3.90 (s, 3H).

Preparation of 4-(4-aminophenoxymethyl)-2-methoxycarbonyl-furan

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 4-(4-nitrophenoxymethyl)-2-methoxycarbonyl-furan was reduced to provide 4-(4-aminophenoxymethyl)-2-methoxycarbonyl-furan. ^{1}H NMR ($CDCl_3$): δ 7.15 (d, 1H, J = 3.5 Hz), 7.05 (t, 1H, J = 8.2 Hz), 6.50 (d, 1H, J = 3.5 Hz), 6.37-6.27 (m, 3H), 5.01 (s, 2H), 3.89 (s, 3H).

7.2.45 Preparation of 6-amino-1-(methoxycarbonyl)methylindazoline



Preparation of 1-(methoxycarbonyl)methyl-6-nitroindazoline

To a solution of 6-nitroindazoline (2.0 g, 12.25 mmole) in dry DMF was added anhydrous K_2CO_3 (1.84 g, 13.31 mmole) and methyl 2-bromoacetate (2.04 g, 13.33 mmole). The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with water and the resulting solid was collected by filtration, washed with excessive water, and air dried. The yellow solid collected was purified by silica gel column chromatography using gradient solvent system to furnish two products. The desired product (1.12 g, 41%) with high R_f value on the TLC in 30% EtOAc : hexanes was collected.

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(Methoxycarbonyl)methyl-6-nitro-indazoline was reduced to provide 6-amino-1-

(methoxycarbonyl)methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 1H, J = 1.1 Hz), 7.35 (d, 1H, J = 8.2 Hz), 6.49 (dd, 1H, J= 1.8 and 8.8 Hz), 6.39 (s, 1H), 5.34 (br s, 2H), 5.10 (s, 2H), 3.64 (s, 3H).

Preparation of 1-(methoxycarbonyl)methyl-5-nitroindazoline

In like manner to the preparation of 1-(methoxycarbonyl)methyl-6-nitroindazoline, 1-(methoxycarbonyl)methyl-5-nitroindazoline was prepared by alkylation of 5-nitroindazoline with methyl 2-bromoacetate in presence of K_2CO_3. The desired product (1.34 g, 46%) with high R_f value on the TLC in 30% EtOAc : hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.75 (d, 1H, J = 1.8 Hz), 8.30 (dd, 1H, J = 2.3 and 8.2 Hz), 8.26 (s, 1H), 7.40 (d, 1H, J = 8.2 Hz), 5.22 (s, 2H), 3.78 (s, 3H).

Preparation of 5-amino-1-(methoxycarbonyl)methylindazoline

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(Methoxycarbonyl)methyl-5-nitro-indazoline was reduced to provide 5-amino-1-(methoxycarbonyl)methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J = 2.3 Hz), 7.15 (d, 1H, J = 8.8 Hz), 6.95 (d, 1H, J= 2.3 Hz), 6.88 (dd, 1H, J = 2.3 and 8.8 Hz), 5.09 (s, 2H), 3.73 (s, 3H).

Preparation of 1-(2-ethoxycarbonylethyl)-6-nitroindazoline

In like manner to the preparation of 1-(methoxycarbonyl)methyl-6-nitroindazoline, 1-(ethoxycarbonyl)ethyl-6-nitroindazoline was prepared by alkylation of 6-nitroindazoline with ethyl 3-bromopropionate in presence of K_2CO_3. The desired product (58%) with high R_f value on the TLC in 30% EtOAc : Hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H), 8.12 (s, 1H), 8.01 (dd, 1H, J = 1.7 and 8.8 Hz), 7.82 (d, 1H, J = 8.8 Hz), 4.74 (t, 2H, J = 6.4 Hz), 4.09 (qt, 2H, J = 7.0 Hz), 3.03 (t, 2H, J = 6.4 Hz), 1.18 (t, 3H, J = 7.0 Hz).

Preparation of 6-amino-1-(2-ethoxycarbonylethyl)indazoline

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(2-ethoxycarbonylethyl)-6-nitroindazoline was reduced to provide 6-amino-1-(2-ethoxycarbonylethyl)indazoline. ^{1}H NMR ($CDCl_3$): δ 7.81 (s, 1H), 7.46 (d, 1H, J = 8.8 Hz),

6.60 (app s, 1H), 6.55 (dd, 1H, J = 2.3 and 8.8 Hz), 4.51 (t, 2H, J = 7.0 Hz), 4.11 (qt, 2H, J = 7.0 Hz), 3.52 (br s, 2H), 2.91 (t, 2H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.0 Hz).

Preparation of 1-(2-ethoxycarbonylethyl)-5-nitroindazoline

In like manner to the preparation of 1-(methoxycarbonyl)methyl-5-nitroindazoline, 1-(ethoxycarbonyl)ethyl-5-nitroindazoline was prepared by alkylation of 5-nitroindazoline with ethyl 3-bromopropionate in presence of K_2CO_3. The desired product (43%) with high Rf value on the TLC in 30% EtOAc : Hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, 1H, J = 1.7 Hz), 8.27 (dd, 1H, J = 2.3 and 8.8 Hz), 8.20 (d, 1H, J = 1.7 Hz), 7.59 (d, 1H, J = 8.8 Hz), 4.70 (t, 2H, J = 6.4 Hz), 4.07 (qt, 2H, J = 7.0 Hz), 3.01 (t, 2H, J = 6.4 Hz), 1.16 (t, 3H, J = 7.0 Hz).

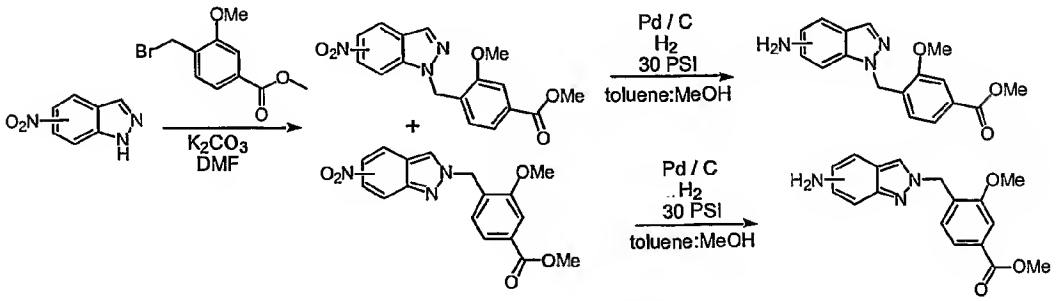
Preparation of 5-amino-1-(2-ethoxycarbonylethyl)indazoline

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 1-(2-ethoxycarbonylethyl)-5-nitroindazoline was reduced to provide 5-amino-1-(2-ethoxycarbonylethyl)indazoline. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.30 (d, 1H, J = 8.8 Hz), 6.91 (d, 1H, J = 2.3 Hz), 6.87 (dd, 1H, J = 2.3 and 8.8 Hz), 4.59 (t, 2H, J = 6.4 Hz), 4.08 (qt, 2H, J = 7.0 Hz), 3.02 (br s, 2H), 2.92 (t, 2H, J = 7.0 Hz), 1.16 (t, 3H, J = 7.0 Hz).

Preparation of 5-amino-2-methylindazoline

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, commercially available 2-methyl-5-nitroindazoline was reduced to provide 5-amino-2-methylindazoline. ^{1}H NMR ($CDCl_3$): δ 7.61 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 6.81 (dd, 1H, J = 2.3 and 8.8 Hz), 6.75 (d, 1H, J = 2.3 Hz), 4.13 (s, 3H), 3.85 (br s, 2H).

7.2.46 Preparation of methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate



In like manner to the preparation of 1-(methoxycarbonyl)methyl-6-nitro-indazoline, methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate was prepared by alkylation of 6-nitroindazoline with methyl (4-bromomethyl)-3-methoxybenzoate in presence of K_2CO_3. The desired product (48%) with high R_f value on the TLC in 30% EtOAc : hexanes was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.50 (d, 1H, J = 1.7 Hz), 8.14 (s, 1H), 8.00 (dd, 1H, J = 1.8 and 8.8 Hz), 7.82 (d, 1H, J = 8.8 Hz), 7.56 (s, 1H), 7.54 (d, 1H, J = 1.8 Hz), 7.07 (d, 1H, J = 8.2 Hz), 5.70 (s, 2H), 3.96 (s, 3H), 3.88 (s, 3H). Low R_f: **Methyl 3-methoxy-4-[(6-nitroindazol-2-yl)methyl]benzoate:** ^{1}H NMR ($CDCl_3$): δ 8.68 (br s, 1H), 8.07 (s, 1H), 7.86 (dd, 1H, J = 1.8 and 9.0 Hz), 7.72 (d, 1H, J = 9.0 Hz), 7.61 (d, 1H, J = 7.7 Hz), 7.58 (s, 1H), 7.19 (d, 1H, J = 7.7 Hz), 5.69 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H).

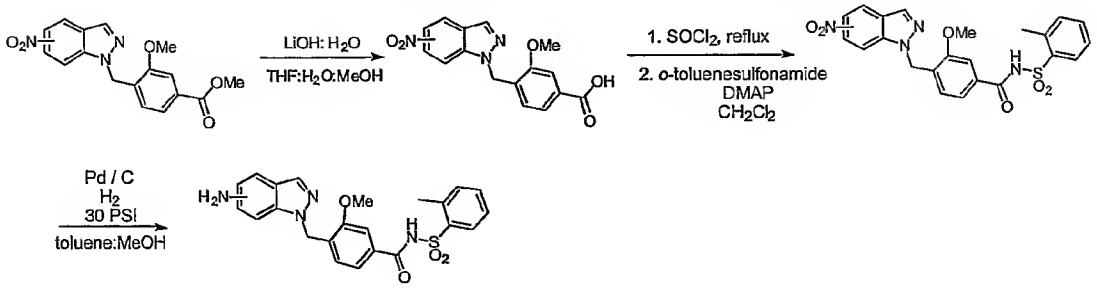
Preparation of Methyl 4-[(6-aminoindazol-1-yl)methyl]benzoate

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate was reduced to provide methyl 4-[(6-aminoindazol-1-yl)methyl]benzoate. ^{1}H NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.53 (d, 1H, J = 8.8 Hz), 7.51 (d, 1H, J = 8.8 Hz), 7.50 (d, 1H, J = 1.7 Hz), 6.67 (d, 1H, J = 8.8 Hz), 6.56 (dd, 1H, J = 1.7 and 8.8 Hz), 6.45 (d, 1H, J = 1.2 Hz), 5.50 (s, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.79 (br s, 2H).

Preparation of Methyl 4-[(6-aminoindazol-2-yl)methyl]benzoate

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, methyl 3-methoxy-4-[(6-nitroindazol-2-yl)methyl]benzoate was reduced to provide methyl 4-[(6-aminoindazol-2-yl)methyl]benzoate. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.56-7.53 (m, 2H), 7.43 (d, 1H, J = 8.8 Hz), 6.98 (d, 1H, J = 8.2 Hz), 6.81 (app s, 1H), 6.58 (dd, 1H, J = 1.8 and 8.8 Hz), 5.53 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H).

7.2.47 Preparation of 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline



Preparation of 6-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy) benzyl]indazoline

Ester hydrolysis of methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate in presence of LiOH:H_2O produced the corresponding acid. The acid (1.65 g, 5.04 mmole) thus formed was converted to the acid chloride by reacting with $SOCl_2$ (3.68 mL, 50.45 mmole) at reflux temperature for 5 h. The reaction mixture was cooled to room temperature and concentrated under vacuo. To acid chloride concentrate dissolved in dry CH_2Cl_2 (75 mL), *o*-toluylbenzenesulfonamide (0.95 g, 5.54 mmole) and 4-(dimethylamino)-pyridine (0.67 g, 5.54 mmole) were added successively at room temperature and stirred for 12 h. The reaction mixture was concentrated, dissolved in EtOAc (700 mL) and successively treated with 2 N HCl (2 X 100 mL), water (150 mL) and brine (100 mL). Usual workup and purification by silica gel column chromatography provided the product (1.57 g, 64%). ^{1}H NMR (DMSO-d_6): δ 8.75 (s, 1H), 8.31 (s, 1H), 8.00 (d, 1H, J = 8.8 Hz), 7.95-7.91 (m, 2H), 7.50 (d, 1H, J = 1.2 Hz), 7.46-7.27 (m, 4H), 6.92 (d, 1H, J = 7.6 Hz), 5.76 (s, 2H), 3.81 (s, 3H), 2.54 (s, 3H).

Preparation of 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline

In like manner to the reduction of diethyl 2-methyl-2-(3-nitrophenoxy)malonate, 6-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline was reduced to provide 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline. ^{1}H NMR ($CDCl_3$): δ 7.96 (dd, 1H, J = 1.2 and 8.2 Hz), 7.76 (s, 1H), 7.51 (d, 1H, J = 1.2 Hz), 7.49-7.44 (m, 1H), 7.37 (d, 2H, J = 8.8 Hz), 7.34-7.32 (m, 1H), 7.30 (d, 1H, J = 8.8 Hz), 6.51-6.47 (m, 2H), 6.35 (s, 1H), 5.35 (s, 2H), 3.89 (s, 3H), 2.54 (s, 3H).

Preparation of methyl 3-methoxy-4-[(5-nitroindazol-1-yl)methyl]benzoate

In like manner to the preparation of methyl 3-methoxy-4-[(6-nitroindazol-1-yl)methyl]benzoate, methyl 3-methoxy-4-[(5-nitroindazol-1-yl)methyl]benzoate was prepared by alkylation of 5-nitroindazoline with methyl (4-bromomethyl)-3-methoxybenzoate in presence of K_2CO_3. The desired product (47%) with high R_f value on the TLC in 30% EtOAc : Hexanes as eluent was collected by silica gel column chromatographic purification. ^{1}H NMR ($CDCl_3$): δ 8.73 (d, 1H, J = 1.8 Hz),8.26-8.22 (m, 2H), 7.56 (s, 1H), 7.54 (dd, 1H, J = 1.8 and 8.2 Hz), 7.49 (d, 1H, J = 9.4 Hz), 6.98 (d, 1H, J = 8.2 Hz), 5.66 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H). Low R_f: Methyl 3-methoxy-4-[(5-nitroindazol-2-yl)methyl]benzoate.

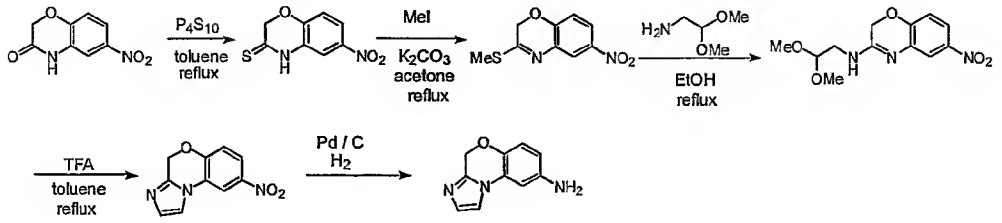
Preparation of 5-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline

In like manner to the preparation of 6-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline, 5-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline was prepared from methyl 3-methoxy-4-[(5-nitroindazol-1-yl)methyl]benzoate. ^{1}H NMR (DMSO-d_6): δ 8.81 (d, 1H, J = 2.3 Hz), 8.39 (s, 1H), 8.21 (dd, 1H, J = 1.8 and 8.8 Hz), 7.87 (dd, 2H, J = 3.6 and 8.8 Hz), 7.48 (d, 1H, J = 1.2 Hz), 7.39 (dd, 1H, J = 1.2 and 8.2 Hz), 7.33-7.15 (m, 3H), 6.85 (d, 1H, J = 8.2 Hz), 5.65 (s, 2H), 3.76 (s, 3H), 2.49 (s, 3H).

Preparation of 5-amino-1-[2-methoxy-4-(*o*-toluyl-sulfonamidocarboxy)benzyl]indazoline

In like manner to the preparation of 6-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline, 5-amino-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline was prepared by reduction of 5-nitro-1-[2-methoxy-4-(*o*-toluylsulfonamidocarboxy)benzyl]indazoline . ^{1}H NMR (DMSO-d_6): δ 7.87 (dd, 1H, J = 1.2 and 7.7 Hz), 7.73 (s, 1H), 7.50 (s, 1H), 7.35-7.14 (m, 5H), 6.78 (d, 1H, J = 1.8 Hz), 6.75 (s, 1H), 6.53 (d, 1H, J = 8.2 Hz), 5.44 (s, 2H), 3.82 (s, 3H), 2.50 (s, 3H).

7.2.48 Preparation of 8-amino-4*H*-imidazo[2,1-*c*][1,4]-benzoxazine



7.3 Synthesis of 2,4-Pyrimidinediamines

A variety of 2,4-pyrimidinediamines of the invention were synthesized from the above starting materials and intermediates and other commercially available reagents. Conditions suitable for synthesizing N2,N4-bis-substituted-2,4-pyrimidinediamine compounds ("general SNAr" reaction conditions; Substitution Nucleophilic Aromatic Reaction) are exemplified with N2,N4-bis(4-ethoxyphenyl)-2,4-pyrimdinediamine (**R926069**) and N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (**R921218**). Conditions suitable for synthesizing asymmetric N2,N4-disubstituted-2,4-pyrimdinediamines are exemplified by N4-(3,4-ethylenedioxyphenyl)-5-fluoro-N2-(3-hydroxyphenyl)-2,4-pyrimidinediame (**R926210**).

7.3.1 N2,N4-Bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (R926069)

To a solution of 2,4-dichloropyrimidine (0.015g, 0.1 mmol) in EtOH (1 mL) was added 4-ethoxyaniline (0.034 g, 0.025 mmol) and heated in a sealed tube at 70-80 °C for 24h. Upon cooling the reaction was diluted with H_2O (10 mL), acidified with 2N HCl, the solid obtained was filtered, washed with H_2O and dried to give N2,N4-bis(4-ethoxyphenyl)-2,4-pyrimidinediamine (**R926069**). ^{1}H NMR (CD_3OD): δ 7.63 (d, 1H), 7.45 (d, 2H), J= 9 Hz), 7.32 (d, 2H, J= 9.3 Hz), 6.95 (d, 2H, J= 6.9 Hz), 6.87 (d, 2H, J= 8.7 Hz), 6.23 (d, 1H, J= 7.2 Hz), 4.04 (m, 4H), 1.38 (m, 6H); LCMS: ret. time: 25.91 min.; purity: 99.5%; MS (m/e): 351 (MH^+).

7.3.2 N2,N4-Bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R921218)

A mixture of 2,4-dichloro-5-fluoropyrimidine (0.0167 g, 0.1 mmol) and 3-aminophenol (0.033 g, 0.3 mmol) in MeOH: H_2O (1.8:0.2 mL; v/v) was shaken in a sealed tube at 100 °C for 24h (or 80 oC for 3 days), cooled to room temperature, diluted with water (15 mL), acidified with 2N HCl (pH >2). Upon saturation with sodium chloride it was

extracted with ethyl acetate (3 x 20 mL), dried over anhydrous sodium sulfate and solvent was removed. The resulting residue was filtered through a pad of silica gel (200-400 mesh) using CH_2Cl_2 - >1 >10% MeOH in CH_2Cl_2 to obtain the desired N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine **(R921218)**. If the reaction scale is large enough, solid of the resulting product can be isolated by filtration. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 1H, J= 5.1 Hz), 7.12-6.90 (m, 6H), 6.64 (dd, 1H, J= 1.8 and 8.1 Hz), 6.53 (dd, 1H, J= 1.2 and 5.7 Hz); LCMS: ret. time: 16.12 min.; purity: 100%; MS (m/e): 313 (MH^+).

7.3.3 N2,N4-Bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926017)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methoxyaniline were reacted to yield N2,N4-bis(4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.67 (d, 1H, J= 4.8 Hz), 7.43 (d, 2H, J= 9.3 Hz), 7.67 (d, 2H, J= 8.7 Hz), 6.87 (d, 2H, J= 9.6 Hz), 6.83 (d, 2H, J= 8.7 Hz), 3.83 (s, 3H), 3.81(s, 3H); LCMS: ret. time: 22.53 min.; purity: 100%; MS (m/e): 341 (MH^+).

7.3.4 N2,N4-Bis(3-fluoro-4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926018)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-fluoro-4-trifluoromethylaniline were reacted to yield N2,N4-bis(3-fluoro-4-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H, J= 3 Hz), 7.77 (m, 3H), 7.61 (dt, 1H, J= 4.2 and 3 Hz), 7.20 (t, 1H, 8.7 Hz), 7.12 (t, 1H, J= 9.3 Hz), 6.95 (s, 1H), 6.82 (s, 1H); ^{19}F NMR ($CDCl_3$): δ –17505 (s, 3F), -17517 (s, 3F), -17525 (s, F), -17537 (s, F), -46835 (s, 1F); LCMS: ret. time: 32.39 min.; purity: 95%, MS (m/e): 453 (MH^+).

7.3.5 N2,N4-Bis(3,4-tetrafluoroethylendioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926037)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-tetrafluoroethylenedioxyaniline were reacted to yield N2,N4-bis(3,4-tetrafluoroethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 1H, J= 3.0 Hz), 7.71 (d, 1H, J= 2.4 Hz), 7.70 (1H, d, J= 2.4 Hz), 7.18 (dd, 2H, J= 2.4 and 6 Hz), 7.07 (d, 2H, J= 1.8 Hz), 7.00 (1H, bs), 6.81 (d, 1H, J= 2.7 Hz); ^{19}F NMR ($CDCl_3$): -

26029 (sept, 8F), -46791 (s, C5-F); LCMS: ret. time: 38.20 min.; purity: 85%; MS (m/e): 541 (MH^+).

7.3.6 N2,N4-Bis(3-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926038)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-trifluoromethoxyaniline were reacted to yield N2,N4-bis(3-trifluoromethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.03 (bd, 1H), 7.62 (bs, 2H), 7.48 (bd, 1H), 7.39 (t, 1H, J= 8.1 Hz), 7.34 (m, 1H), 7.29 (t, 1H, J= 7.5 Hz), 7.01 (m, 2H), 6.88 (m, 2H); ^{19}F NMR ($CDCl_3$): -16447 (s, 3F), –16459 (s, 3F), -46738 (s, 1F); LCMS: ret. time: 33.77 min.; purity: 93%; MS (m/e): 449 (MH^+).

7.3.7 N2,N4-Bis(4-chloro-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926039)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloro-3-trifluoromethylaniline were reacted to yield N2,N4-bis(4-chloro-3-trifluoromethylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.05 (bs, 1H), 7.89 (bd, 1H), 7.77 (dd, 1H, J= 2.4 and 9 Hz), 7.65 (dd, 1H, J= 2.4 and 8.7 Hz), 7.49 (d, J= 8.1 Hz), 7.40 (d, 1H, J= 6.2 Hz), 7.03 (s, 1H), 6.91 (s, 1H); ^{19}F NMR ($CDCl_3$): δ –17864 (s, 3F), -17894 (s, 3F), -46550 (s, 1F); LCMS: ret. time: 38.81 min.; purity: 75%; MS (m/e): 485 (MH^+).

7.3.8 N2,N4-Bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926064)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-ethoxyaniline were reacted to yield N2,N4-bis(3-ethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.96 (1H, d, J= 4.8 Hz), 7.22 (m, 6H), 7.07 (t, 1H, J= 1.8 Hz), 6.95 (dt, 1H, J= 1.2 and 7.2 Hz), 6.77 (m, 2H), 3.88 (q, 4H, J= 6.3 Hz), 1.33 (two t, 6H, J= 6.3 Hz); ^{19}F NMR ($CDCl_3$): -46175; LCMS: ret. time: 26.86 min.; purity: 97%; MS (m/e): 369 (MH^+).

7.3.9 N2,N4-Bis(3-hydroxy-4-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926339)

In like manner to to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methoxylaniline were reacted to yield N2,N4-bis(3-hydroxy-4-methoxyphenyl)-5-fluoro--2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.82 (d, 1H J= 4 Hz), 7.18 (m, 2H), 6.95 (m, 2H), 6.83 (m, 2H) 3.93 (s, 6H); LCMS: ret. time: 16.63 min.; purity: 97 %; MS (m/e): 373 (MH^+).

7.3.10 N2,N4-Bis(4-ethoxycarbonylamino-3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926340)

In like manner to to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-ethoxycarbonylamino-3-hydroxyaniline were reacted to yield N2,N4-bis(4-ethoxycarbonylamino-3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.86 (d, 1H J= 4 Hz), 7.67 (m, 2H), 7.20 (dd, 1H, J= 8 Hz, J= 4.1 Hz), 7.13 (d, 1H), 6.90 (m, 2H), 4.2(m, 4H), 1.32 (m, 6H); LCMS: ret. time: 20.92 min.; purity: 98 %; MS (m/e): 487 (MH^+).

7.3.11 N2,N4-Bis(-3-hydroxy-4-methylphenyl)-5-fluoro-2,4-pyrimidinediaminediamine (R926341)

In like manner to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-hydroxy-4-methylaniline were reacted to yield N2,N4-bis(-3-hydroxy-4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.83 (d, 1H J= 4 Hz), 7.11 (m, 4H), 6.81 (m, 2H), 2.19 (m, 6H); LCMS: ret. time: 20.69 min.; purity: 98 %; MS (m/e): 341 (MH^+).

7.3.12 N2,N4-Bis[4-(2-methoxyethyleneoxy)phenyl]-5-fluoro--2,4-pyrimidinediamine (R926342)

In like manner to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-(2-methoxyethyloxy)aniline were reacted to yield N2,N4-bis[4-(2-methoxyethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.89 (d, 1H J= 4 Hz), 7.54 (dd, 2H, J= 6.8 and 2.7 Hz), 7.38 (dd, 2H, J= 6.8 and 2.7 Hz), 6.87 (dd, 2H, J= 6.8 and 2.7 Hz), 6.82 (dd, 2H, J= 6.8 and 2.7 Hz) 4.6 (m, 4H), 4.11 (m, 4H), 3.35 (m, 6H); LCMS: ret. time: 21.76 min.; purity: 97 %; MS (m/e): 429 (MH^+).

7.3.13 N2,N4-Bis(dihydrobenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediaminediamine (R909237)

In like manner to N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 5-amino-2,3-dihydrobenzofuran were reacted to yield N2,N4-bis(dihydrobenzofuran-5-yl)-5-fluoro-2,4-pyrimidinediaminediamine. ^{1}H NMR (CD_3OD): δ 7.99 (d, 1H J= 4 Hz), 7.22 (m, 4H), 6.81 (m, 2H), 4.55 (m, 4H), 3.22 (m, 4H); LCMS: ret. time: 23.80 min.; purity: 98 %; MS (m/e): 438 (MH^+).

7.3.14 N2,N4-Bis(3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926065)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-methoxyaniline were reacted to yield N2,N4-bis(3-methoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.96 (d, 1H, J= 5.4 Hz), 7.24 (m, 6H), 7.06 (t, 1H, J= 2.4 Hz), 7.00 (dt, 1H, J= 1.2 Hz), 6.79 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H); ^{19}F NMR (CD_3OD): δ - 46112; LCMS: ret. time: 23.46 min.; purity: 99%; MS (m/e): 341 (MH^+).

7.3.15 N2,N4-Bis[4-(N,N-dimethylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926086)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-N,N-dimethylaniline were reacted to yield N2,N4-bis[4-(N,N-dimethylamino)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 1H, J= 3.6 Hz), 7.43 (d, 2H, J= 8.7 Hz), 7.34 (d, 2H, J= 8.7 Hz), 7.25 (s, 1H), 6.73 (m, 4H), 6.55 (s, 1H), 2.95 (s, 6H), 2.90 (s, 6H); ^{19}F NMR ($CDCl_3$): - 47770; LCMS: ret. time: 12.48 min.; purity: 99%; MS (m/e): 367 (MH^+).

7.3.16 N2,N4-Bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926109)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-ethylenedioxyaniline were reacted to yield N2,N4-bis(3,4-ethylenedioxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J= 3.6 Hz), 7.23 (d, 1H, J= 2.3 Hz), 7.15 (d, 1H, J= 2.4 Hz), 7.00 (dd, 1H, J= 3 and 8.1 Hz), 6.98 (dd, 1H, J= 3 and 8 Hz), 6.83 (d, 1H, J=8.7 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.7(s, 1H), 6.58 (s, 1H), 4.23 (m, 4H), 4.24(m, 4H); ^{19}F NMR ($CDCl_3$): δ - 47445; LCMS: ret. time: 21.81 min.; purity: 96%; MS (m/e): 397 (MH^+).

7.3.17 N2,N4-Bis(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926110)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3,4-dimethoxyaniline were reacted to yield N2,N4-bis(3,4-dimethoxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 1H, J= 1.8 Hz), 7.13 (d, 2H, J= 4.8 Hz), 7.08 (d, 1H, J= 8.7 Hz), 6.94 (d, 2H, J= 10.5 Hz), 6.81 (d, 1H, J= 8.7 Hz), 6.76 (d, 1H, J= 8.7 Hz), 6.70 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3..71 (s, 3H); ^{19}F NMR ($CDCl_3$): δ - 47433; LCMS: ret. time: 19.64 min.; purity: 95%; MS (m/e): 401 (MH^+).

7.3.18 N2,N4-Bis[4-(N-morpholino)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926114)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-N-morpholinylaniline were reacted to yield N2,N4-bis[4-N-morpholinyl)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 7.80 (s, 1H), 7.78 (s, 1H, partially exchanged), 7.76 (bs, 1H, partially exchanged), 7.53 (d, 2H, J= 8.1 Hz), 7.39 (d, 2H, J= 9 Hz), 6.93 (d, 2H, J= 8.7 Hz), 6.86 (bd, 2H), 3.84 (m, 8H), 3.11 (m, 8H); ^{19}F NMR (CD_3OD): δ - 47697; LCMS: ret. time: 18.15 min.; purity: 99.55%; MS (m/e): 451 (MH^+).

7.3.19 N2,N4-Bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926206)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-chloroaniline were reacted to yield N2,N4-bis(4-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 7.80 (d, 1H, J= 4.2 Hz), 7.45 (d, 2H, J= 8.7 Hz), 7.33 (d, 2H, J= 9 Hz), 7.20 (d, 2H, J= 8.7 Hz), 7.14 (d, 2H, J= 9.6 Hz); LCMS: ret. time: 28.84 min.; purity: 87%; MS (m/e): 349 (MH^+).

7.3.20 N2,N4-Bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926209)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloroaniline were reacted to yield N2,N4-bis(3-chlorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR (CD_3OD): δ 8.08 (d, 1H, J= 5.4 Hz), 7.70 (t, 1H, J= 1.8 Hz), 7.57 (t, 1H, J= 1.2 Hz), 7.54 (m, 1H), 7.35

(m, 4H), 7.28 (t, 1H, J= 1.8 Hz), 7.24 (m, 1H), 7.22 (t, 1H, J= 1.8 Hz); ^{19}F NMR (CD_3OD): - 43631; LCMS: ret. time: 28.99 min.; purity: 99%; MS (m/e): 349 (M^+).

7.3.21 N2,N4-Bis(4-tert-butylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926222)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-tert-butylaniline were reacted to yield N2,N4-bis(4-tert-butylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.77 (d, 1H, J= 3.9 Hz), 7.47 (d, 2H, J= 9Hz), 7.38 (m, 4H), 7.30 (d, 2H, J= 8.7 Hz), 1.34 (s, 9H), 1.32 (s, 9H); LCMS: ret. time: 34.09 min.; purity: 93%; MS: 393 (MH^+).

7.3.22 N2,N4-Bis(3-chloro-4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926223)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-chloro-4-fluoroaniline were reacted to yield N2,N4-bis(3-chloro-4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$ + CD_3OD)): δ 7.81 (d, 1H), 7.60 (m, 1H), 7.58 (m, 1H), 7.38 (m, 1H), 7.19 (m, 1H), 7.0 (m, 2H); LCMS: ret. time: 28.98 min.; purity: 97%; MS (m/e): 385 (M^+).

7.3.23 N2,N4-Bis(4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine (R926224)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-fluoroaniline were reacted to yield N2,N4-bis(4-fluorophenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 8.79 (d, 2H, J= 5.4 Hz), 7.40 (m, 2H), 7.30 (m, 2H), 6.90 (m, 4H); ^{19}NMR ($CDCl_3$): - 32425 (s, 1F), -32940 (s, 1F), -45525 (s, 1F); LCMS: ret. time: 23.53 min.; purity: 100%; MS (m/e): 317 (MH^+).

7.3.24 N2,N4-Bis(4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926225)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 4-methylaniline were reacted to yield N2,N4-bis(4-methylphenyl)-5-fluoro-2,4-pyrimidinediamine. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, 1H, J= 4.2 Hz), 7.43 (d, 2H, J= 8.1 Hz), 7.36 (d, 2H, J= 8.4 Hz), 7.14 (d, 2H, J= 8.4

Hz), 7.10 (d, 2H, J= 8.1 Hz), 2.39 (s, 3H), 2.35 (s, 3H); LCMS: ret. time: 25.81 min.; purity: 99.65%; MS (m/e): 309 (MH^+).

7.3.25 N2,N4-Bis[(4-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926240)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 4-aminophenoxyacetate were reacted to yield N2,N4-bis[(4-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR (CD_3OD): δ 7.8 (bs, 1H), 7.50 (d, 2H, J= 9.3 Hz), 7.32 (d, 2H, J= 8.41 Hz), 6.88 (m, 4H), 4.72 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H); ^{19}F NMR ($CDCl_3$): -47570; LCMS: ret. time: 21.17 min.; purity: 95%; MS (m/e): 457 (MH^+).

7.3.26 (±)-N2,N4-Bis[4-methoxycarbonyl(α-methyl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine (R926254)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and (±)-ethyl 2-(4-aminophenoxy)propionate were reacted to yield (±)-N2,N4-bis[4-methoxycarbonyl(α-methyl)methyleneoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.89 (bs, 1H), 7.48 (dd, 2H, J= 2.4 and 6.9 Hz), 7.40 (dd, 2H, J= 1.8 and 6.9 Hz), 6.85 (m, 4H), 6.76 (s, 1H), 6.63 (s, 1H), 4.75 (hex, 2H, J= 6.3 Hz), 3.77 (s, 3H), 3.76 (s, 3H), 1.62 (t, 6H, J= 7.5 Hz); LCMS: ret. time: 23.76 min.; purity: 97%; MS (m/e): 485 (MH+).

7.3.27 N2,N4-Bis[(3-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine (R926255)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and ethyl 3-aminophenoxyacetate were reacted to yield N2,N4-bis[(3-methoxycarbonylmethyleneoxy)phenyl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.96 (d, 1H, J= 2.4 Hz), 7.71 (t, 1H, J= 2.4 Hz), 7.44 (m, 2H), 7.21 (m, 3H), 6.96 (dd, 1H, J= 1.2 and 7.8 Hz), 6.86 (d, 1H, J= 3 Hz), 6.53 (m, 1H), 4.64 (s, 2H), 4.60 (s, 2H), 3.79 (s, 6H); LCMS: ret. time: 21.72 min.; purity: 87%; MS (m/e): 457 (MH^+).

7.3.28 N2,N4-Bis(3-acetyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926387)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-acetoxyaniline were reacted to yield N2,N4-bis[(3-acetoxyphenyl]-5-fluoro-2,4-pyrimidinediamine. Alternatively, N2,N4-bis[(3-acetoxyphenyl]-5-fluoro-2,4-pyrimidinediamine can be prepared by acetylation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine with acetyl chloride in the presence of pyridine in CH_2Cl_2. ^1H NMR ($CDCl_3$): δ 8.00 (bs, 1H), 7.51-7.25 (m, 8H), 2.32 (s, 3H), 2.28 (s, 3H); LCMS: ret. time: 22.14 min; purity: 100%; MS (m/e): 397 (MH^+).

7.3.29 N2,N4-Bis(3-benzyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine (R926394)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 3-benzyloxyaniline were reacted to yield N2,N4-bis(3-benzyloxyphenyl)-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 7.98 (bs, 1H), 7.42-6.99 (m, 16H), 6.75 (d, 1H, J= 2.4 Hz), 6.71 (m, 1H), 6.60 (dd, 1H, J= 2.4 and 8.4 Hz), 6.32 (m, 1H), 4.97 (s, 2H), 4.94 (s, 2H); LCMS: ret. time: 32.56 min.; purity: 98%; MS (m/e): 493 (MH^+).

7.3.30 N2,N4-Bis(2-phenylphenyl)-5-fluoro-2,4-pyrimidinediamine (R926398)

In like manner to the preparation of N2,N4-bis(3-hydroxyphenyl)-5-fluoro-2,4-pyrimidinediamine, 2,4-dichloro-5-fluoropyrimidine and 2-phenylaniline were reacted to yield N2,N4-bis[(2-phenylphenyl]-5-fluoro-2,4-pyrimidinediamine. ^1H NMR ($CDCl_3$): δ 8.35 (m, 1H), 8.0 (s, 1H), 7.85 (s, 1H), 7.45-7.00 (m, 18H); LCMS: ret. time: 30.29 min.; purity: 68%; MS (m/e): 433 (MH^+).

7.3.31 (R926404) N2, N4-Bis(2-phenylphenyl)-5-methyl-2,4-pyrimidinediamine

In like manner to the preparation of 5-fluoro-N2,N4-bis(3-hydroxyphenyl)-2,4-pyrimidinediamine, 2-aminobiphenyl and 2,4-dichloro-5-methylpyrimidine were reacted to provide N2, N4-bis(2-phenylphenyl)-5-methyl-2,4-pyrimidinediamine. LCMS: ret. time: 30.47 min.; purity: 91%; MS (*m/e*): 429 (MH^+).